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CRYPTOCOCCOSIS

Report of a Case and Experimental Studies

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LOS ANGELES

CRYPTOCOCCOSIS is a relatively rare disease, approximately 100 cases having been reported to date. It is characterized by invasion of the body by yeastlike organisms which have a special affinity for the lungs and central nervous system. Clinical manifestations are those of a subacute or chronic infection. Pathologically the response of the tissue is similar to that seen in other infectious granulomas.

The disease was first described by Frothingham,[1] who reported its occurrence in a horse. The first report of the disease in man is that of Stoddard and Cutler,[2] who published their monograph in 1916. There have been numerous reports since that time. Some of the more recent reviews include one by Reeves, Butt and Hammack[3] in 1941 and one by Voyles and Beck[4] in 1946.

The causative organism, Cryptococcus hominis, is widely distributed in nature as a saprophyte. It is a yeastlike organism which reproduces by budding only, without mycelial or endospore formation. In tissue the parasites are seen intracellularly surrounded by vacuoles.

Clinical manifestations vary with the site and extent of involvement. Systemic involvement includes, in order of decreasing frequency, the central nervous system, lungs, spleen, liver, kidneys, mesenteric nodes and ileum. The signs and symptoms are those of toxemia in association with those produced by destructive processes in involved organs. There may be a slight rise in temperature, with corresponding increase in pulse. Headache is the most common initial symptom along with various mental symptoms.

1. Frothingham, L.: A Tumor-Like Lesion in the Lung of a Horse Caused by Torula, J. M. Research **9**:31, 1902.

2. Stoddard, J. L., and Cutler, E. C.: Torula Infection in Man, Monograph 6, Rockefeller Institute for Medical Research, 1916.

3. Reeves, D. L.; Butt, E. M., and Hammack, R. W.: Torula Infection of the Lungs and Central Nervous System, Arch. Int. Med. **68**:57-79 (July) 1941.

4. Voyles, G. Q., and Beck, E. M.: Systemic Infection Due to Torula Histolytica, Arch. Int. Med. **77**:504-525 (May) 1946.

The pathologic lesion [5] consists of a small nodule from 0.5 to 0.8 mm. in diameter. The microscopic structure is that of miliary tubercles with absence of polymorphonuclear leukocytes. The organism occurs both intracellularly and extracellularly.

In the central nervous system there is chronic leptomeningitis, with thickening of the meninges and adhesions to the cortex. There is little exudation, but tubercles may be seen scattered through the brain substance. Two kinds of lesions are seen: one, a granulomatous perivascular lesion; the other, small nodules, tubercles or gelatinous cystlike structures scattered throughout the cerebral tissues. Microscopically these lesions have small spherical spaces filled with gelatinous material in which are embedded many cryptococci. There is insignificant cellular reaction about these lesions and only slight increase in glial tissue in the neighborhood of the focus. There are many monocytes and lymphocytes in and about the lesions, but in general the picture is that of solution of brain substance by the parasite without adequate inflammatory reparative processes.

In most cases of cryptococcosis the condition has been diagnosed and described at autopsy. Even when the diagnosis has been made before death the disease usually runs a subacute or chronic course which leads to inevitable death. To date no satisfactory therapeutic agent has been provided although numerous ones have been tried.[6]

We have been fortunate in being able to follow a patient previously reported on.[3] She has lived for nine years since the onset of symptoms. Five years have passed since the previous report. Sulfonamide compounds have provided the basis for her treatment throughout this period.

The experiments reported in this article were undertaken to evaluate the treatment given and to guide future therapy.

REPORT OF A CASE

A. C. L., a 14 year old white girl, first became ill in August 1937. At that time her symptoms consisted of headache, nausea, vomiting, failing vision, slight fever and a productive cough.

She was first examined at the Carmichael Hospital for Tropical Diseases at Calcutta, India, where neurologic examination was noncontributory and lumbar puncture revealed slightly increased pressure. Roentgenograms of her chest

5. Jacobson, H. P.: Fungous Disease, Springfield, Ill., Charles C Thomas, Publisher, 1932, pp. 253-279. Gay, F. P.: Agents of Disease and Host Resistance, ibid., 1935, pp. 1109-1151. Conant, N. F., and others: Manual of Clinical Mycology, Philadelphia, W. B. Saunders Company, 1945, pp. 111-125.

6. Marshall, M., and Teed, R. W.: Torula Histolytica Meningo-Encephalitis: Recovery Following Bilateral Mastoidectomy and Sulfonamide Therapy, J. A. M. A. **120**:527-529 (Oct. 17) 1942. Tinney, W. S., and Schmidt, H. W.: Torula Infection, M. Clin. North America **28**:950-956 (July) 1944.

revealed empyema of the right interlobar area, which was explored surgically and found to consist mainly of fibrous tissue with signs of chronic inflammation. No organisms were recovered. A draining sinus persisted at the site of the operation.

In December 1937 the spinal fluid pressure was 290 mm. and the fluid contained many polymorphonuclear cells and gave a positive Wassermann reaction but yielded no organisms. The reaction to a Wassermann test of the blood was questionably positive. Roentgenograms of the skull revealed a beaten silvery appearance, with increased convolutional markings. Ophthalmoscopically, both optic disks were pale, particularly that of the right eye.

In February 1938 a craniotomy was performed in the right frontal area. The brain was found to be under increased intracranial pressure, but no abscess was found.

In April 1938 the patient entered the Hospital of the Good Samaritan in Los Angeles under the care of Dr. Robert Cunningham and Dr. Roy Hammack.

At this time the appearance was that of a pale, apathetic, emaciated white girl of about 15 years. A well healed craniotomy scar was evident, and the sinus in the chest was still draining. The optic disks had the appearance of primary atrophy. Besides constricted visual fields, no other neurologic changes were detected. The blood pressure was 120 systolic and 80 diastolic. Roentgenograms of the chest in June 1938 revealed an area of density, extending upward and outward from the right hilus, which occupied the anterior part of the chest and appeared to involve the interlobar fissure. A roentgenogram of the skull demonstrated the healed craniotomy wound as well as considerable accentuation of the convolutional markings. The hemoglobin content was 67 per cent, the red blood cell count 4,010,000 and the white blood cell count 7,100, with 65 per cent polymorphonuclear cells and 25 per cent lymphocytes. A Wassermann test of the blood gave a negative reaction. Lumbar puncture revealed a pressure of 200 mm., with 73 cells per cubic centimeter (predominantly polymorphonuclear cells) and 175 mg. of protein per hundred cubic centimeters. The reaction of the spinal fluid to a Wassermann test was negative. The colloidal gold curve was 5555554211. Cryptococcus hominis was observed on smear and grown on culture of the material drained from the sinus in the chest. The organism was also grown in a culture of the spinal fluid. After this the patient was discharged to her home. She was taking 15 grains (0.97 Gm.) of potassium iodide daily.

Second Admission.—The patient was admitted nine months later for reexamination. She felt stronger and had gained 17 pounds (7.7 Kg.). Headache was still present, and C. hominis was cultured from the spinal fluid. The lesion in the chest had decreased in size roentgenologically. She received a ten day course of sulfapyridine, during which time the blood sulfapyridine level ranged between 9 and 13 mg. per hundred cubic centimeters.

Third Admission.—The patient reentered the hospital in May 1939, and the only noteworthy change was an increase in strength. Organisms were still recoverable from the sinus in the chest and from the spinal fluid. A ten day course of sulfanilamide was started, a blood concentration of between 9 and 12 mg. per hundred cubic centimeters being maintained.

Fourth Admission.—By December 1939 she had gained 15 pounds (6.8 Kg.) and felt much improved. Roentgen examination showed further decrease of the lesion in the chest. Lumbar puncture showed a pressure of 200 mm., with 46 cells per cubic centimeter and 225 mg. of protein per hundred cubic centimeters. Cryptococcus hominis was again cultured from the spinal fluid. She was given undenatured Torula antigen (Kreuger) and has continued using 1.0 cc. twice weekly since that time.

Fifth Admission.—The patient had improved sufficiently to attend a school for the blind until September 1941, and in October she was readmitted complaining of headache and dizziness. The physical and neurologic condition was unchanged. The blood pressure was now 150 systolic and 100 diastolic. Cryptococcus hominis could no longer be cultured from the sinus in the chest but was recovered from the spinal fluid. Sulfadiazine was given for twelve days, with the blood concentration ranging between 10 and 13 mg. per hundred cubic centimeters. The patient left the hospital improved after two weeks.

Sixth and Seventh Admissions.—The sixth and seventh admissions cover the period from October 1943 to October 1944. On both occasions the patient was admitted because of signs and symptoms of increased intracranial pressure. The symptoms were alleviated by lumbar puncture and rest in bed. On neither occasion was C. hominis cultured from the spinal fluid, and no specific treatment was attempted.

Eighth Admission.—In July 1945 the patient was readmitted because of recurrence of headache and vomiting. Lumbar puncture demonstrated increased pressure, cells and protein. The colloidal gold curve was 133433210. Cryptococcus hominis was cultured from the spinal fluid. She was again started on sulfadiazine, and she continued to take the drug for a period of six weeks, during which time the blood sulfadiazine level was maintained between 7.8 and 10.9 mg. per hundred cubic centimeters.

Ninth, Tenth and Eleventh Admissions.—The ninth, tenth and eleventh admissions cover the period from October 1945 to February 1946. The patient was admitted for study and sulfadiazine therapy. The physical condition remained unchanged, and the blood pressure was 160 systolic and 100 diastolic. Neurologic examination now showed an increase of the deep tendon reflexes. The sinus in the chest remained dry. Lumbar puncture showed increased pressure, cells and protein. Culture of the spinal fluid did not reveal any cryptococci, nor did numerous cultures of the urine. Urinalysis showed only a trace of albumin. The blood sulfadiazine level was maintained at 14 to 17 mg. per hundred cubic centimeters on two occasions for two week periods of therapy.

Twelfth Admission.—The patient reentered the hospital in May 1946 for further study and treatment. There were no complaints, and the blood pressure was 160 systolic and 106 diastolic. Ophthalmoscopically, the picture of advanced optic atrophy was seen. A check of the visual fields showed the right eye to be entirely unreliable, and lack of central vision in the left eye made it impossible to outline the blindspot and adjacent blind areas. Electroencephalographic study showed a persistently abnormal wave pattern over both frontal and temporal lobes. The abnormality consisted of slow waves of 3 and 6 cycles per second combined with rapid waves of 17 to 19 cycles per second. The amplitude of these abnormal wave patterns often came close to or exceeded 100 microvolts. This type of abnormality was felt to be consistent with cortical irritation on account of pressure. There were no focal signs. The nonprotein nitrogen was 27 mg. per hundred cubic centimeters, urea clearance 73 per cent, albumin 5.2 Gm. and globulin 2.0 Gm. Culture of the urine did not reveal any cryptococci. The kidneys, ureter and bladder were normal.

The patient was started on another course of sulfadiazine therapy, but administration of the drug had to be discontinued on the fourth day on account of hematuria. Accordingly, sulfanilamide was tried, but this was soon withheld because of excessive nausea and vomiting. At no time was there any evidence of depression of the bone marrow from the use of either drug.

The patient was discharged to her home and is being followed in the outpatient department.

EXPERIMENT

In order to evaluate various therapeutic agents in the treatment of cryptococcosis, the following experiments were performed: A preliminary study was made to determine the pathogenicity of the organism. A five month old culture of the patient's spinal fluid was used as the source for organisms. This was subcultured on plates of modified agar-plain agar with 5 per cent dextrose and 0.5 per cent tartaric acid. Culture plates were washed with sterile isotonic solution of sodium chloride to provide a suspension of cryptococcus organisms. Twenty million organisms thus obtained were inoculated intraperitoneally into white rats. Animals of this group were followed for fifty days. It was found that the organism being used produced only localized lesions in test animals. These lesions consisted of

TABLE 1.—*Length of Survival of Animals After Infection with Cryptococcosis*

Animal Group	Average Days of Survival After Infection
Preinfected and untreated	6.2
Healthy and untreated	11.4
Healthy and treated with sulfadiazine	28.9
Healthy and treated with penicillin	22.6
Healthy and treated with sulfadiazine and penicillin	22.1
Healthy and treated with streptomycin	28.0
Healthy and inoculated with antigen	13.1

TABLE 2.—*Pathologic Findings in Twenty-Five Animals at Postmortem Examination*

Peritonitis	52%
Visceral abscesses	24%
Abdominal lymphadenopathy	20%
Empyema	16%
Pericarditis	8%
Pneumonia	8%
Subcutaneous nodules	8%
Meningitis	4%

subcutaneous nodules, involvement of lymph nodes and omental masses. Only a negligible number of animals succumbed to the cryptococcic infection. Accordingly, a number of animals were killed. The involved tissues were macerated with a sterile mortar and pestle and cultured on dextrose-tartaric acid agar. Three serial passages through white rats were then performed. Organisms obtained fom the final passage were used in later experiments. After the third serial animal passage culture plates were washed with sterile isotonic solution of sodium chloride. The suspension of C. hominis thus obtained contained 1.3 billion organisms per cubic centimeter. Animals in the experiment were inoculated intraperitoneally with 0.5 cc. of this suspension (650,000,000 organisms). The animals used were white rats weighing 150 to 200 Gm. These animals may be grouped as follows:

1. Five animals who had been infected in the preliminary experiment with 20,000,000 original organisms but who showed no clinical evidence of disease were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. These animals received no treatment.

Five healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. These animals received no treatment.

2. Ten healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. Four days later treatment with sulfadiazine sodium in 0.1 cc. of sterile isotonic solution of sodium chloride subcutaneously every four hours was started and was continued for twelve days. From then until the eighteenth day they received 0.006 Gm. in 0.2 cc. of sodium chloride every six hours. Treatment was abandoned at that time and the animals observed.

3. Eight healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. Four days later treatment with penicillin sodium was started. Each animal received subcutaneously 50 units of penicillin (285 units per kilogram) dissolved in 0.1 cc. of sterile isotonic solution of sodium chloride every four hours for twelve days. From then until the eighteenth day they received 100 units of penicillin in 0.2 cc. of sodium chloride every six hours. Treatment was then abandoned and the animals observed for further changes.

4. Eight healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. Four days later treatment was started with penicillin and sulfadiazine in combination. Each animal received 0.003 Gm. of sulfadiazine sodium in 0.1 cc. of isotonic solution of sodium chloride plus 50 units of penicillin sodium in 0.1 cc. of sodium chloride as two separate subcutaneous injections every four hours for twelve days. From then until the eighteenth day they received 0.006 Gm. of sulfadiazine sodium in 0.2 cc. of sodium chloride plus 100 units of penicillin sodium in 0.2 cc. of sodium chloride subcutaneously every six hours. Treatment then was abandoned and the animals observed for further changes.

5. Ten healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. Four days later treatment was started with streptomycin. Each animal received 950 units of streptomycin sulfate (approximately 5,590 units per kilogram) in 0.1 cc. of sterile isotonic solution of sodium chloride subcutaneously every four hours for twelve days. From then until the eighteenth day each animal received 1,900 units of streptomycin sulfate in 0.2 cc. of sterile isotonic solution of sodium chloride every six hours. Treatment was then abandoned and the animals observed for further changes.

6. Eight healthy animals were inoculated intraperitoneally with 0.5 cc. of standard suspension of cryptococci. These animals received by subcutaneous injection 0.1 cc. of standard cryptococcus antigen (Kreuger) which had been diluted 1:60 with sodium chloride on the fourth, sixth and eighth days after infection. They were observed for further changes.

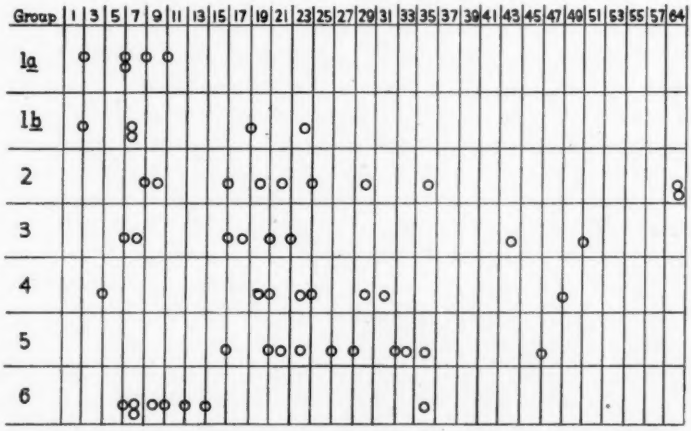
COMMENT

The results of the animal experiments conducted would indicate that sulfadiazine or streptomycin will prolong life expectancy in cryptococcosis. Penicillin afforded slight advantage, and there was no benefit noted in combining penicillin and sulfadiazine. It might be of value at a later date to determine if any advantage would accrue from combining sulfadiazine and streptomycin. Another factor of importance but unfortunately not covered by the present experiments is that of fluid balance. The amount of isotonic solution of sodium chloride used to dissolve the drugs employed would approximate 500 cc. daily

for the adult weighing 70 kilograms. This may be an important factor in prolonging life.

Animals which had been preinfected lived no longer than the control group. Animals untreated save for administration of vaccine lived no longer than the control group. These results might be taken to indicate that there is but slight tendency to form protective antibodies against the organism.

As regards the course of the disease in the patient discussed, she has long passed the life expectancy for persons afflicted with this disease. The lesion in her chest has definitely improved in the past several years, as evidenced by decrease in its size and decrease in amount of secretion. No organism has been recovered from the sinus in her chest for over five years. Changes in the central nervous system have



Days of survival after infection. (Marks refer to individual animals.)

not been as progressive as one might expect them to be if the disease process were active. In the past three years culture of the spinal fluid has yielded cryptococci on only one occasion, which was a year ago.

It is of interest to note the development of hypertension in this patient. We believe that it is accounted for best on a basis of internal hydrocephalus, with increased intracranial pressure.

The role of sulfonamide compounds in this patient's disease is difficult to evaluate. We believe, however, that the course has been greatly modified by use of the drug.

SUMMARY

1. Animals previously infected with the cryptococcus and clinically appearing well gave no sign of having developed antibody protection against that organism.

Animals treated with sulfadiazine had their life expectancy increased from 11.4 to 28.9 days.

Animals treated with penicillin had their life expectancy increased from 11.4 to 22.6 days.

No advantage accrued when penicillin and sulfadiazine were used in combination.

Animals treated with streptomycin had their life expectancy increased from 11.4 to 28.0 days.

Vaccination as employed in this experiment did not appreciably alter the life expectancy of the animals used.

2. The course of the cryptococcic infection in the patient reported on would seem to have been altered by sulfonamide therapy.

COMPLETE ATRIOVENTRICULAR BLOCK IN DIPHTHERITIC MYOCARDITIS

Report of a Case with Serial Electrocardiographic Tracings

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REVIEW OF THE ENGLISH LITERATURE, 1901 TO 1946

UNTIL recently, partial atrioventricular block in diphtheria has been recognized rarely and detailed serial studies of complete atrioventricular block in diphtheria have been scarce. It was difficult to ascertain from the literature the first reported cases of heart block of any degree, because undoubtedly some occurred which were unrecognized for want of technologic apparatus. White and Smith reviewed 946 cases of diphtheria in 1904 studied at the Boston City Hospital, and in 3 of these pulse rates "to 30 or even 20" were present; these undoubtedly were cases of complete heart block, but electrocardiographic technics were not available to the authors.

First and Second Degree Atrioventricular Block.—As Stecher noted, at least 2 instances of partial heart block in diphtheria have been reported before 1938, 1 by Hume in 1913 and 1 by Hecht, cited by Marvin, in 1924. Since 1938, Burkhardt and others and Neubauer have reported a total of 36 cases of partial heart block in diphtheria. The absence of reported cases of this lesion prior to that time probably was due to the fact that they were not recognized, since only by means of the electrocardiogram can the diagnosis of partial heart block be confirmed.

Complete Atrioventricular Block.—Sprague and White described a case, first observed in 1907, in which high grade heart block was due primarily to tonsillar diphtheria. Smith in 1921 observed no instances of low grade heart block but 10 instances of complete heart block in 242 consecutive cases of diphtheria. In 1937 Begg wrote: "A characteristic of diphtheritic lesions of the main bundle of His is that complete atrioventricular dissociation appears usually without pre-

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liminary changes in the P-R interval." This seems to be a phenomenon unique in myocarditis caused by Corynebacterium diphtheriae. In other cases of complete heart block the condition commonly progresses through the lesser degrees first. Begg's series of cases of severe faucial diphtheria comprised 100, in none of which was first or second degree heart block demonstrable. He observed that the usual sequence was "some abnormality in the ventricular portion of the tracing and then, suddenly, complete dissociation."

In 1938 Burkhardt, Eggleston and Smith reported on 140 cases, gathered over a period of one and one-half years, of toxic diphtheria. In 28 of these there were graphic changes in the electrocardiogram. In 17 cases conduction changes developed between the fifth and the thirteenth day of illness. Atrioventricular dissociation was manifested in 11 of these,

TABLE 1.—*Reported Cases of Diphtheritic Heart Block*

Authors	Year	Total Number of Cases	Number of Cases of Heart Block	
			Incomplete	Complete
Sprague and White	1907	1	0	1
Hume	1913	1	1	0
Jones and White	1915	2	0	2
Parkinson	1915	1	0	1
Smith	1921	242	0	10
Hecht	1924	1	1	0
Stecher	1928	19	0	19
Burkhardt and others (28 of 140 showed electrocardiographic changes)	1938	17	6	11
Neubauer	1943	44	30	14
Givhan and Mahon	1945	10	1	0
Stimson	1946	1	0	1

and all 11 were fatal. Autopsies were performed in 7 cases, and Burkhardt and his co-authors felt that "there was a rough parallelism between the conductivity as shown by the electrocardiograph and the microscopic changes in the myocardium. Many cases showing atrioventricular dissociation presented a terminal picture of ventricular tachycardia."

HYPERTOXIC TONSILLOPHARYNGEAL DIPHTHERIA

Our case [1] was one of fatal hypertoxic tonsillopharyngeal diphtheria occurring in a 17 year old white youth, in whom myocardial damage was manifested four days after the onset of the illness. Detailed serial electrocardiographic study was undertaken in an attempt to observe the progress of heart block in this disease. The major electrocardiographic features developing during the course of the illness were as follows:

1. The clinical and therapeutic aspects are published in detail in Walker, W.; Massey, F., and Mostofi, K.: Streptomycin-Resistant Diphtheria, J. A. M. A. **135**:771 (Nov. 22) 1947.

(1) intraventricular block; (2) complete atrioventricular heart block with a progressively decreasing ratio of ventricular to auricular contractions; (3) shifting of the cardiac axis to the right; (4) terminal increased intraventricular block; (5) progressive diminution in amplitude of QRS complexes, and (6) appearance of what appeared to be interpolated premature auricular beats. The electrocardiographic tracing of June 3 showed intraventricular block (QRS measuring 0.12 second) but no impaired atrioventricular conduction (P-R interval, 0.16 second). Because of technical difficulties at this time, only lead I was obtainable, and the single tracing is not reproduced in this paper for that reason. The cardiac rate was 96 per minute. On the following day complete atrioventricular block developed, giving rise to a tracing manifesting a complex arrhythmia. A detailed inspection of the records obtained

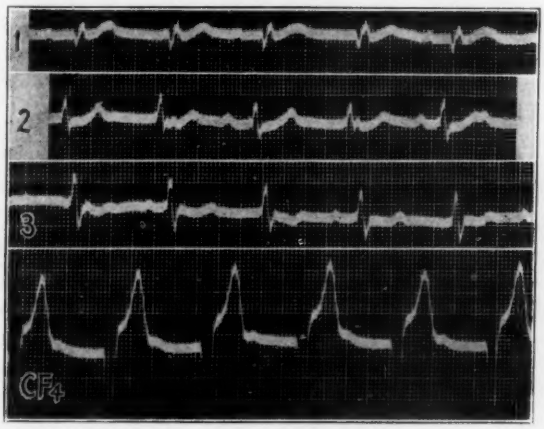

Fig. 1.—Electrocardiogram of June 4, 1946. The auricular rate is 102 per minute, and the ventricular rate is 68 per minute. Complete atrioventricular block is present.

affords an excellent opportunity to study the progressive involvement by the diphtheritic infection of the cardiac conduction system and the myocardium.

Progressive Electrocardiographic Changes.—There are two features of the electrocardiogram of June 4 (fig. 1) which identify it as revealing a complete atrioventricular block. The first of these is the fact that the ventricular complexes occur at regular intervals. This distinguishes the condition immediately from partial atrioventricular block with irregular ventricular response. The second diagnostic feature is the fact that the P waves are not fixed in their relationship to the ventricular complexes, which differentiates this from a partial atrioventricular block

with regular ventricular response. The auricular rate is 102 per minute. The ventricular rate is 68 per minute.

Irregularity of ventricular beating does occur in complete atrioventricular block in these circumstances: (1) when there is a shifting of the idioventricular pacemaker, (2) in the presence of premature ventricular systoles and (3) when there is arrhythmia of a single idioventricular pacemaker. The first of these is demonstrated in the tracing of June 9 (fig. 5) and the second in the tracing of June 5 (fig. 2). The record of June 5 also is identifiable as showing complete atrioventricular block by the fact that the P waves are not fixed in their position in the ventricular premature contractions. The presence of intraventricular block may be assumed, since the QRS complexes measured 0.12 second

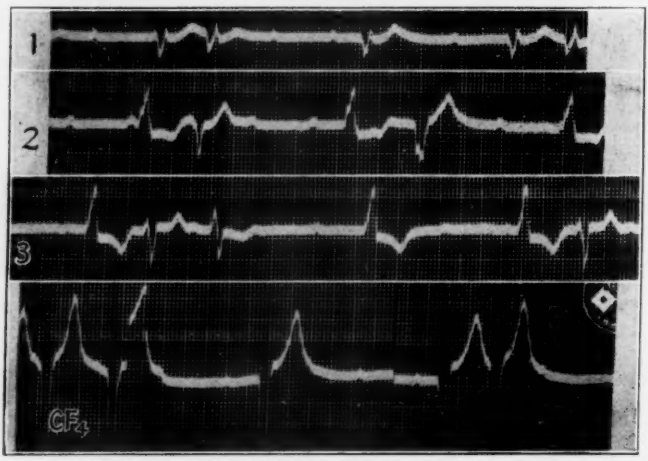

Fig. 2.—Electrocardiogram of June 5, 1946. Complete atrioventricular block complicated by the appearance of premature ventricular contractions. The auricular rate is 104 per minute, and the ventricular rate is 52 per minute.

on June 3, prior to the appearance of atrioventricular block. Ventricular ectopic contractions from several foci at times produce a coupled rhythm. The auricular rate is 104 per minute. The ventricular rate is 52 per minute.

In the tracings of June 6 (fig. 3) the features of complete atrioventricular block are again apparent, with occasional ventricular ectopic contractions. On the assumption that the idioventricular pacemaker has remained stationary between June 4 and 6, this tracing shows a pronounced shifting of the cardiac axis to the right. Also, there has been elevation of the S-T segment in lead I and inversion of the T waves with depression of the S-T segments in leads II and III.

Tracings taken later on the same day showed a mechanism basically similar to that in these electrocardiograms.

On June 7 (fig. 4) the ventricular rate decreased from 50 to 42 per minute. The auricular rate was 96 per minute. Elevation of the S-T

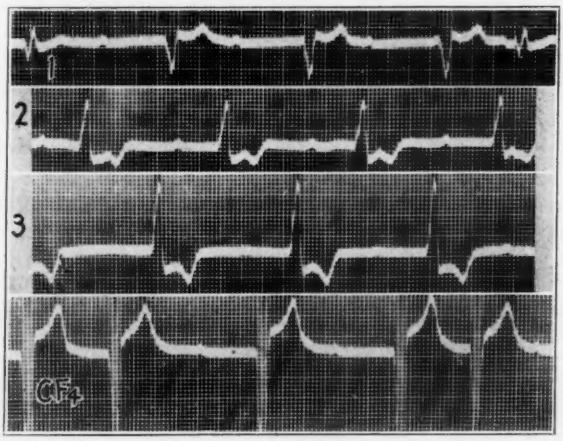

Fig. 3.—Electrocardiogram of June 6, 1946. Complete atrioventricular block with notable deviations in the S-T segment. The auricular rate is 98 per minute, and the ventricular rate is 50 per minute.

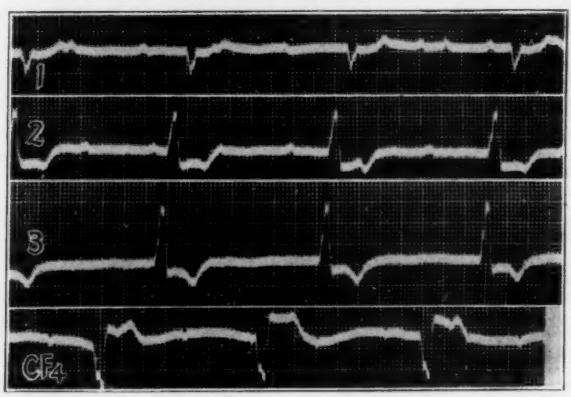

Fig. 4.—Electrocardiogram of June 7, 1946. Auricular rate is decreased to 96 per minute and the ventricular rate reduced to 42 per minute. Marked depression of the S-T segments in leads II and III is seen, with elevation of the S-T segment in lead CF_4. The QRS interval measures 0.12 second.

segment in lead I had disappeared, but depression of the S-T segments persisted in leads II and III, with comparable elevation in lead CF_4.

The QRS interval measured 0.12 second. What appeared to be an interpolated auricular premature beat was noted in lead I (between the third and fourth ventricular complexes).

By June 9 (fig. 5) the ventricular rate had slowed remarkably to 34 per minute while the auricular rate remained relatively constant at 98. Since the tracing of June 7 the changes in the S-T segment and in the T waves in leads II and III essentially had disappeared. The elevated S-T segment in CF_4 was not as extreme as in the tracings of June 7 (fig. 5). This tracing is notable for the presence of two idioventricular pacemakers. This produced a coupled rhythm shown best in leads III and CF_4.

Decrease of the ventricular rate to 26 per minute, with an auricular rate averaging 104 at 10:45 p. m. is the outstanding feature of the record of June 11 (fig. 6). The QRS interval is widened to 0.16 second.

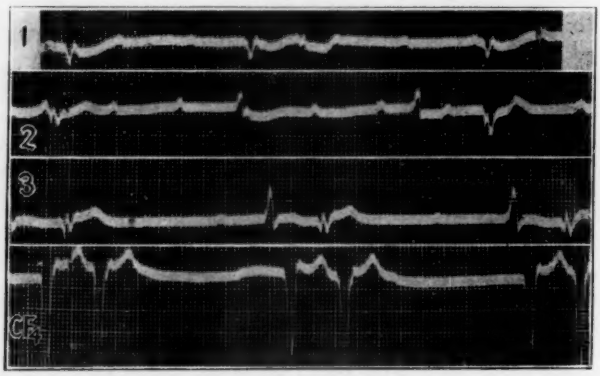

Fig. 5.—Electrocardiogram of June 9, 1946. The auricular rate is 98 per minute, while the ventricular rate has slowed still further to 34 per minute. Coupling is manifested.

Further return to normalcy of the S-T segments is present. There has been some decrease in voltage of the QRS complexes. In lead CF_4 two ventricular contractions occur in such rapid succession that they nearly superimpose their QRS inscriptions. What appear to be interpolated auricular premature beats again are seen in leads II and III of this tracing. This was the last electrocardiogram, obtained just prior to death, which occurred six hours later.

OBSERVATIONS AT AUTOPSY

Gross Changes.—Pertinent findings at necropsy included 1,000 cc. of clear, straw-colored fluid in the peritoneal cavity, with the liver extending 9 cm. below the xiphoid in the midline and 1 cm. below the

costal margin in the right anterior axillary line. Each pleural cavity contained 400 cc. of clear, straw-colored fluid.

The heart weighed 420 Gm. and was found lying transversely in situ, with the right border formed almost entirely of the enlarged right atrium, Anteriorly, the cardiac mass was made up of the hypertrophied, dilated right ventricle. Posteriorly, a small left ventricle was found. The left atrium was small.

Numerous petechiae were seen on the epicardium, but it was smooth and glistening as was the endocardium, which showed no hemorrhage. Measurement of the wall of the left ventricle showed it to be 1.8 cm. thick; the wall of the right ventricle was 0.4 cm. thick. The myocardium had a mottled, purplish brown appearance, and it was soft. The valves were unremarkable, and the coronary vessels were normal.

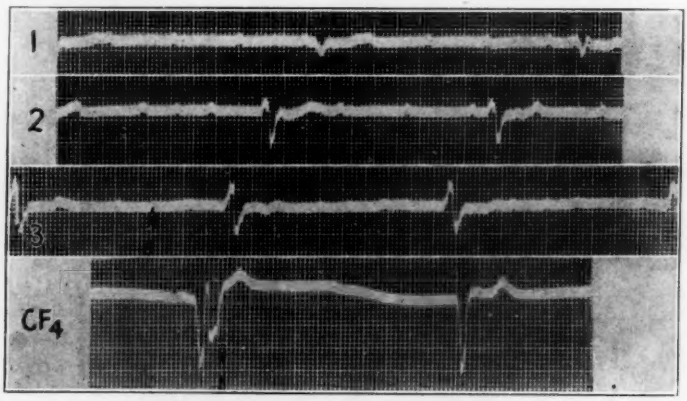

Fig. 6.—Electrocardiogram of June 11, 1946—just prior to the patient's death. The auricular rate at this time was 104 per minute but the ventricular rate has dropped still further to 26 per minute. Intraventricular block, with a QRS interval of 0.16 second, is seen.

Histopathologic Process.—Extensive myocarditis was apparent, the myocardial fibers, specially those of the ventricle, showing edema and notable degenerative changes. These alterations included cloudy swelling, fragmentation and vacuolization, hyaline degeneration, loss of nuclei and complete destruction of many muscle fibers to a degree at which only debris filled the sarcolemma. Other myocardial fibers had been replaced entirely by loose fibrous tissue. Although widespread, these changes were patchy, leaving isolated groups of muscle fibers unaffected by the process. Frequently associated with the necrotic areas and occasionally independent of them were infiltrations of inflammatory cells including monocytes, plasma cells, lymphocytes and some polymorphonuclear

leukocytes and eosinophils. Macrophages and multinucleated giant cells were also seen. In a few areas, especially in the wall of the left ventricle and in the periatrioventricular nodal region, the focal accumulation of inflammatory cells was so dense that it simulated abscess formation.

Section of the periatrioventricular nodal region particularly showed advanced degeneration of the muscle fibers in the midst of intense cellular infiltration. The sinoatrial node was less involved. Atrial pathologic change was not as great.

Fig. 7.—Gross specimen of the heart and pericardium, showing numerous petechial hemorrhages.

COMMENT

While it is obvious that the highly specialized function of the myocardial fibers (atrial and ventricular), that is, contractility, was tremendously impaired, it is also plausible to assume that the conducting tissues lost much of their ability to transmit stimuli with normal rapidity. As a result of progressive inflammatory-toxic changes, irreparable damage was wrought.

As borne out by histopathologic examination, the atrial musculature was less severely impaired than the ventricular, which possibly is a contributory factor for the phenomenon of the progressively diminishing ventricular rate despite a relatively constant atrial rate. Conduction itself was hampered considerably, and this was the prime basis for the advent of complete heart block and prior intraventricular block.

Clinically, right ventricular failure was evident two days before death, but pathologic enlargement of the right side of the heart occurred and was reflected in the electrocardiographic pattern before this time. Hepatic congestion and ascites were demonstrated clinically, and the diagnosis was confirmed at autopsy. Peripheral edema was not present.

SUMMARY

1. A survey of the English literature on the subject of heart block in myocarditis caused by Corynebacterium diphtheriae is presented which indicates that partial atrioventricular block was rarely recognized until recently and that serial electrocardiographic studies of complete atrioventricular block are few.

2. A detailed analysis is made of a complex arrhythmia with complete atrioventricular block and a progressively decreasing ventricular rate occurring in a case of hypertoxic tonsillopharyngeal diphtheria.

3. Observations at autopsy indicated that in a general way the lesions produced by the disease were reflected directly in the serial electrocardiographic studies.

TABLE 2.—*Progressively Decreasing Ratio of Ventricular to Auricular Contractions*

Date	Auricular Rate	Ventricular Rate
June 3	96	96
June 4	102	68
June 5	104	52
June 6	98	50
June 7	96	42
June 9	98	34
June 11	104	26

Colonel Albert H. Robinson, Medical Corps, Tacoma, Washington, and Lowell L. Lane, M.D., Philadelphia, assisted in the preparation of this paper.

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LIPOMELANOTIC RETICULAR HYPERPLASIA OF LYMPH NODES

Report of Six Cases

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THE ASSOCIATION of a peculiar type of hyperplasia of lymph nodes with chronic dermatitis was first pointed out by Pautrier and Woringer [1] in 1937. They reported 11 cases in which there were dermatitis and lymphadenopathy. In 4 instances lymph nodes were removed and showed a peculiar type of hyperplasia. The dermatitis varied in type and degree but was usually erythematous, desquamative and associated with pruritus. The lymph node hyperplasia was characterized by the multiplication of reticular cells, the presence of intracellular fat and melanin pigment and slight infiltration with eosinophils. In 1941 Soloff [2] reported a case in which there were similar changes in the inguinal lymph nodes in a patient who died of disseminated miliary tuberculosis.

It should be noted that in many of the reported cases there was widespread lymphadenopathy, which led to a clinical diagnosis of lymphoblastoma.

In this paper 6 cases of chronic dermatitis, pruritus and lymphadenopathy are reported, and the gross and microscopic features of lipomelanotic reticular hyperplasia of lymph nodes are described.

REPORT OF CASES

CASE 1.—P. F., a 59 year old Negro, was first admitted to the hospital on July 24, 1943, because of a cutaneous eruption and pruritus.

For the previous ten years he had had an eruption on the exposed parts of his body during the months from April to August. The affected skin showed

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From the Institute of Pathology, Western Reserve University, Cleveland, Ohio, and the department of pathology of Northwestern University and Wesley Memorial Hospital.

1. Pautrier, L. M., and Woringer, F.: Contribution à l'étude de l'histo-psysiologie cutanée; à propos d'un aspect histo-pathologique nouveau du ganglion lymphatique: la réticulose lipo-mélanique accompagnant certaines dermatoses généralisées; les échanges entre la peau et le ganglion, Ann. de dermat. et syph. **8**:256-273, 1937.

2. Soloff, L. A.: Lipomelanotic Reticular Hyperplasia of Lymph Nodes: Report of a Case, J. Lab. & Clin. Med. **27** (pt. 1):343-346, 1941.

increased pigmentation, scaling and thickening, and there was an accompanying pruritus of moderate degree. During the fall and winter the skin gradually regained its normal color and texture. Several years after he first noticed the cutaneous lesions a series of scratch tests were done to determine the presence or absence of sensitivity to many common flowers. Several of these gave positive reactions. During the year preceding the admission to the hospital he worked on a small farm and did not come in contact with any of the flowers to which he was said to be sensitive. Early in May he noticed the usual eruption appearing on his face, arms and hands. Shortly before he came to the hospital the eruption spread to involve his entire body.

Physical examination on admission revealed that the temperature was 37.3 C. (99 F.), the pulse rate 80, the respirations 20 and the blood pressure 150 systolic and 100 diastolic. The patient was well developed and well nourished. The skin of the face, neck and arms showed a notable increase in pigmentation, thickening, scaling and edema. Similar changes were present but to a less degree on the trunk and the lower part of the legs. The liver was palpable 3 fingerbreadths below the right costal margin. There was slight pitting edema of the lower part of the legs. The rest of the examination revealed nothing abnormal.

Laboratory examination at the time of admission showed a trace of albumin in the urine, 4,800,000 red blood cells, with a hemoglobin content of 95 per cent (Sahli), and 12,200 white blood cells (50 per cent neutrophils, 48 per cent lymphocytes and 2 per cent monocytes). The reaction to the Kline test was negative.

On his second day in the hospital a small area of skin on the posterior aspect of the thorax was exposed for one and a half minutes to a mercury vapor lamp at a distance of 30 inches (76 cm.). In twenty-four hours this site was erythematous, and in forty-eight hours the skin was edematous and small papules were evident. This reaction was evident for several days, after which pigmentation increased in amount.

The cutaneous lesions improved markedly when treated with calamine ointment and potassium permanganate baths. The patient was discharged on the ninth day in the hospital. The clinical diagnosis was chronic actinic dermatitis due to sensitivity to ultraviolet rays.

He was readmitted to the hospital on Sept. 5, 1944, with a similar pruritic cutaneous eruption. Since his previous admission he had noticed multiple nodules in the groins, left forearm and right knee.

Physical examination on his second admission revealed that the temperature was 37.6 C. (99.6 F.), the pulse rate 88, the respirations 14 and the blood pressure 190 systolic and 100 diastolic. The skin of the arms, axillas, abdomen and thighs was markedly indurated. The axillary and inguinal lymph nodes were moderately enlarged, firm and nontender. In the dermis of the left forearm and of the outer aspect of the right knee there were firm nodules up to 3 cm. in diameter.

On the second admission the urine was normal. The red blood cells numbered 3,860,000, with a hemoglobin content (Sahli) of 84 per cent, and the white blood cells 12,600 (49 per cent neutrophils, 35 per cent lymphocytes, 2 per cent monocytes and 14 per cent eosinophils).

On his second day in the hospital a biopsy of a nodule on the left forearm was done. The surgical specimen consisted of a piece of colored skin and subcutaneous tissue with a maximum measurement of 2 cm. The epidermis was distinctly increased in thickness and showed diffuse hyperkeratinization, patchy parakeratosis and diffuse acanthosis. The dermis was increased in thickness,

fibrotic and infiltrated with many lymphocytes, large mononuclear cells and a few eosinophils. The subcutaneous tissue showed similar fibrosis and cellular infiltration (fig. 1).

On his twelfth day in the hospital a lymph node in the left inguinal area was removed. The surgical specimen consisted of an enlarged lymph node with a maximum diameter of 2.5 cm. This was slightly softer than usual and sectioned with decreased resistance, and it had a bulging pale yellow cut surface. Microscopic examination revealed a few lymph follicles, which in most instances had secondary centers. These follicles were farther apart than usual because of the

Fig. 1 (case 1).—Slight hyperplasia of epidermis. Infiltration of upper part of dermis with lympocytes, large mononuclear cells and eosinophils. Hematoxylin and eosin; × 225.

large number of reticular cells in the cortex (fig. 2). Similar reticular cells of large size with pale eosinophilic and vacuolated cytoplasm were abundant in the medulla. Some of these large reticular cells contained sudanotropic droplets, and in many there was granular dark brown pigment, which because of its solubility in hydrogen peroxide was identified as melanin (fig. 3). Eosinophils were present in moderate number. The diagnosis was lipomelanotic reticular hyperplasia of lymph nodes.

The skin was treated with two courses of superficial roentgen irradiation (75 r), which resulted in considerable relief of the pruritus. A 5 per cent solution of ammoniated mercury ointment was also used. At the time of discharge, on the eighteenth day in the hospital the skin was much softer and the itching was slight.

CASE 2.—B. H., a 48 year old white woman, was admitted to the hospital on Dec. 6, 1944, with the complaint of "marked itching of the skin." Her illness began eight months before, when she noticed a purple macular rash in the right groin. This was treated with roentgen irradiation and disappeared. Similar macular lesions appeared in the left groin, and they disappeared with similar

Fig. 2 (case 1).—Portion of cortex of lymph node with many large reticular cells and no lymph follicles. Pigment (melanin) in reticular cells. Hematoxylin and eosin: × 100.

treatment. A short time later lesions appeared on the scalp, neck, thorax and abdomen. Vesicles also developed, and in July 1944 pruritus became pronounced. At this time she was treated in the dispensary. The history revealed a loss of 30 pounds (13.6 Kg.) in weight during the previous six months. A diagnosis of seborrheic dermatitis was made.

Physical examination on admission revealed a temperature of 37.4 C. (99.3 F.), a pulse rate of 88, respirations 24 and a blood pressure of 150 systolic and 105

diastolic. The patient was poorly developed and obviously undernourished, and she appeared to be chronically ill. The skin was dry, with poor turgor and patchy glistening and scaly areas. Vesicles were present in both inguinal regions, and there were fissures behind the ears. The hair was decreased in amount over the vertex of the scalp. The cervical axillary, epitrochlear and inguinal lymph nodes were increased in size and were firm and nontender. The remainder of the examination was noncontributory.

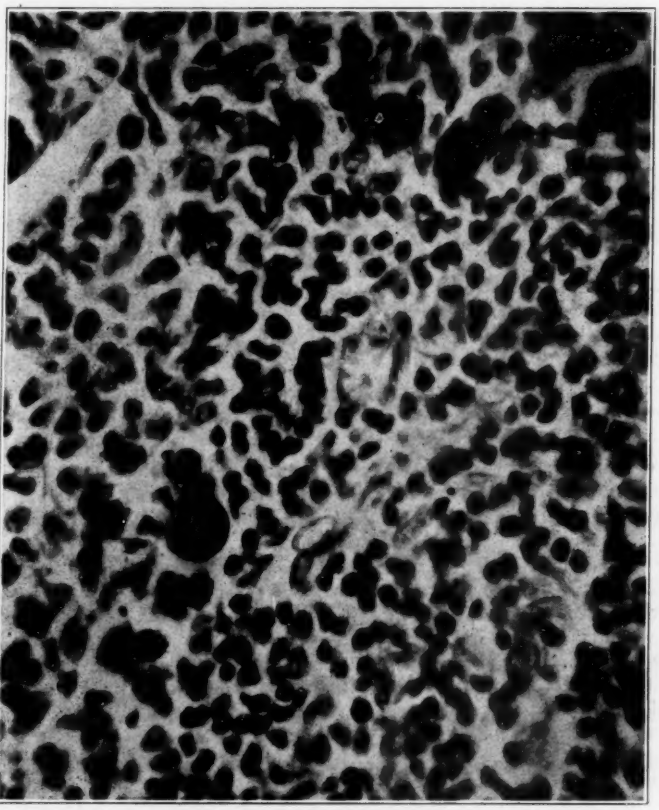

Fig. 3 (case 1).—Reticular cells containing pigment (melanin) in substance of lymph node. Hematoxylin and eosin; × 750.

Laboratory examination on admission showed the urine to be normal. The red blood cell count was 3,230,000, with a hemoglobin content (Sahli) of 74 per cent, and the white blood cell count 6,350 (63 per cent neutrophils, 22 per cent lymphocytes, 7 per cent monocytes and 7 per cent eosinophils). There was a negative reaction to the Kline test.

Course in the Hospital.—She was given potassium permanganate baths (1:10,000) twice daily. Cottonseed oil was also used on the skin, and zinc stearate powder was applied to "weeping" areas. On many occasions she exhibited

depressive symptoms. She was examined by a neuropsychiatrist, who made a diagnosis of "psychoneurosis with reaction depression."

The white blood cell count varied between 5,650 and 7,800. The basal metabolic rate was + 12 per cent.

On her fifth day in the hospital a biopsy was performed, the tissue consisting of a small elliptic piece of white skin. The epidermis was moderately increased in thickness and showed slight parakeratosis and acanthosis. The upper part of the dermis was infiltrated with a moderate number of lymphocytes and large mononuclear cells and an occasional eosinophil. The diagnosis was chronic dermatitis.

On her seventh day in the hospital two of the inguinal lymph nodes were removed. At this time the clinical diagnosis was lymphoblastoma, probably Hodgkin's disease. The surgical specimen consisted of two lymph nodes with maximum measurements of 1 and 1.5 cm. Microscopic examination (fig. 4) revealed the architectural patterns of the lymph nodes to be preserved. The lymph follicles in the cortex were slightly enlarged, and many had distinct secondary centers. Eosinophils were present in moderate numbers throughout the cortical and medullary portions. In the medullary portions there were numerous large mononuclear cells with faintly eosinophilic and, in many instances, vacuolated cytoplasm. Some of these cells contained brown pigment that was soluble in hydrogen peroxide, and many contained sudanotropic droplets. The diagnosis was "lipomelanotic reticular hyperplasia of lymph nodes."

The patient was discharged on the twenty-fifth day in the hospital. At this time she showed moderate improvement, and the clinical diagnosis was seborrheic dermatitis of the scalp and widespread exfoliative dermatitis.

CASE 3.—F. S., a white man aged 56 years, was admitted to the hospital on Jan. 2, 1945. He was a tire maker in a rubber plant and had been working with synthetic rubber for two years. He had been in good health until five months prior to hospitalization, when an erythematous papular eruption developed on the skin of both legs. This was patchy in distribution and was diagnosed as eczema by his private physician. When the eruption became widespread he was referred to a dermatologist. At this time the history revealed slight loss of weight, increasing irritability, excessive perspiration and tremor of the hands. His basal metabolic rate was +50, but his pulse was normal. After treatment of the cutaneous lesions with roentgen rays (three or four times), an ointment and one of the sulfanamide compounds, there was no improvement. The pruritus became severe.

Physical examination at the time of admission revealed a temperature of 37.5 C. (99.5 F.), a pulse rate of 82, a respiratory rate of 25 and a blood pressure of 140 systolic and 90 diastolic. He was normally developed and slightly undernourished. There was widespread erythema, thickening, scaling and excoriation of the skin. The thyroid was not enlarged. The axillary and inguinal lymph nodes on the right and left sides were enlarged (measuring 1 to 3 cm. in maximum diameter), firm, discrete, freely movable and slightly tender. The cervical lymph nodes were similarly enlarged, though to a lesser degree. The thorax was not unusual except for a moderate increase in the anteriorposterior diameter. The heart was normal. There was a fine tremor of the hands. Small anal fissures and internal hemorrhoids were noted.

Laboratory examination at the time of admission showed the urine to be normal. The red blood cell count was 5,100,000, with 98 per cent hemoglobin (Sahli), and the white blood cell count 10,300 (79 per cent neutrophils, 11 per cent

lymphocytes, 5 per cent monocytes, 5 per cent eosinophils and 1 per cent basophils). The reaction to the Kline test was negative, and the plasma cholesterol level was 198 mg. per hundred cubic centimeters.

Course in the Hospital.—The cutaneous eruption was treated with boric acid ointment (1: 5,000), potassium permanganate baths, 5 per cent bismuth tribromphenate, 10 per cent liquid carbonic detergents and irradiation. On two occasions the trunk was treated with 50 r, and on one occasion the hands and arms were treated with 50 r.

On the eleventh day in the hospital his temperature suddenly rose to 39 C. (102.2 F.). At this time there developed hoarseness, a productive cough and

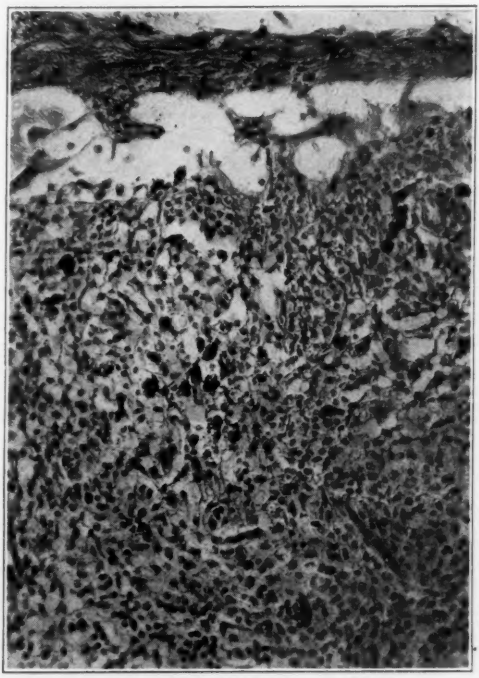

Fig. 4 (case 2).—Abundance of large reticular cells in the cortex of a lymph node, some containing melanin. Hematoxylin and eosin; × 250.

signs of bilateral bronchopneumonia. He was given a total of 400,000 units of penicillin over a period of three days. The signs and symptoms of the respiratory infection disappeared in six days, and it was thought that at the same time there was a distinct improvement in the cutaneous eruption. He was therefore given an additional 500,000 units of penicillin over a period of five days, but there was no further change in the cutaneous lesions.

While he was in the hospital many laboratory examinations were done. At the time of the respiratory infection his white blood cell count was elevated to 27,550 and the urine contained a small amount of albumin and a few white blood cells. A glucose tolerance test gave a normal reaction. His basal metabolic

rate was constantly elevated, varying between +23 and +65. The total plasma protein content was 5.04 Gm., with albumin 3.00 Gm. and globulin 2.04 Gm. per hundred cubic centimeters.

On his third day in the hospital a biopsy of the skin of the right forearm showed moderate hyperplasia of the epidermis, with hyperkeratinization, parakeratosis and acanthosis. There was also moderate cellular infiltration of the upper part of the dermis. The infiltrate consisted of many lymphocytic and large mononuclear cells and a few eosinophils.

On his seventh day in the hospital one of the lymph nodes in the left inguinal area was removed. The surgical specimen consisted of a lymph node 1.8 cm. in maximum measurement. Its consistency and resistance to section were slightly reduced. The cut surface was soft and pale yellow. Microscopic examination showed relatively few small, widely separated lymph follicles. Large reticular cells with pale eosinophilic and vacuolated cytoplasm were numerous in both the cortex and the medulla (fig. 5). Intracellular dark brown pigment (fig. 6), soluble in hydrogen peroxide, was abundant, and a few eosinophils were present. These changes are typical of lipomelanotic reticular hyperplasia of lymph nodes.

The cutaneous eruption improved slightly, and he gained some weight before being discharged on his fifty-third day in the hospital.

CASE 4.—M. P., a 56 year old white woman, was first admitted to the hospital on Jan. 10, 1945, because of a rash of two years' duration.

Her illness began two years prior to her hospitalization while she was working in a tailor shop. She first noticed itching of the skin of the hands, forearms and face. Shortly afterward pruritic erythematous papules appeared, and these sites became roughened and scaly. After the onset of her illness she was examined by her private physician, who made a diagnosis of monocytic leukemia with cutaneous involvement. Her cutaneous lesions were treated symptomatically with numerous ointments, and she was also given sixteen roentgen ray treatments (75 r each) over a two year period.

Physical examination at the time of admission revealed a temperature of 37.4 C. (99.3 F.), a pulse rate of 80, a respiratory rate of 18 and a blood pressure of 146 systolic and 90 diastolic. The patient was well developed and moderately obese. The skin showed widespread erythema and thickening and numerous excoriations. The pharynx was slightly reddened, and the tonsillar tissue was slightly increased in amount. The axillary and inguinal lymph nodes were considerably increased in size and were firm, discrete and nontender. The largest node was in the right axilla and measured 5 cm. in diameter. A systolic murmur was heard in the third right intercostal space. This was transmitted downward but not into the neck. There was also a systolic murmur at the apex, and the second aortic sound was acentuated. No cardiac enlargement could be demonstrated by percussion. No abdominal organs were palpable. There was slight pitting edema of the lower extremities.

At the time of admission the urine contained albumin (0 to 1 plus) and 10 to 40 white blood cells per high power field in sediment. The red blood cell count was 4,960,000, with a hemoglobin content of 100 per cent (Sahli), and a white blood cell count of 12,350 (54 per cent neutrophils, 12.5 per cent lymphocytes, 10 per cent monocytes, 1 per cent eosinophils, 20.5 per cent abnormal [monocytoid] cells and 2 per cent blastocytes). The reaction to the Kline test was negative.

Course in the Hospital.—The skin was treated with tannic acid, witch hazel and boric acid ointment. The axillas and the right groin were also treated with roentgen radiation (200 r).

Additional laboratory examinations revealed a white cell count of 10,300, with a differential count of 45.5 per cent neutrophils, 12 per cent lymphocytes, 7.5 per cent monocytes, 0.5 per cent eosinophils and 34.5 per cent abnormal cells. The abnormal cells were identified as large monocytoid cells. "Their nuclei were made up of chromatin in granular strands, frequently showing segmentation. A few of the cells had two nuclei. The cytoplasm of the abnormal cells was slate grayish blue, nontransparent and frequently vacuolated. Some of the cells had pseudopods. The erythrocytes showed slight variation in size and shape. Platelets

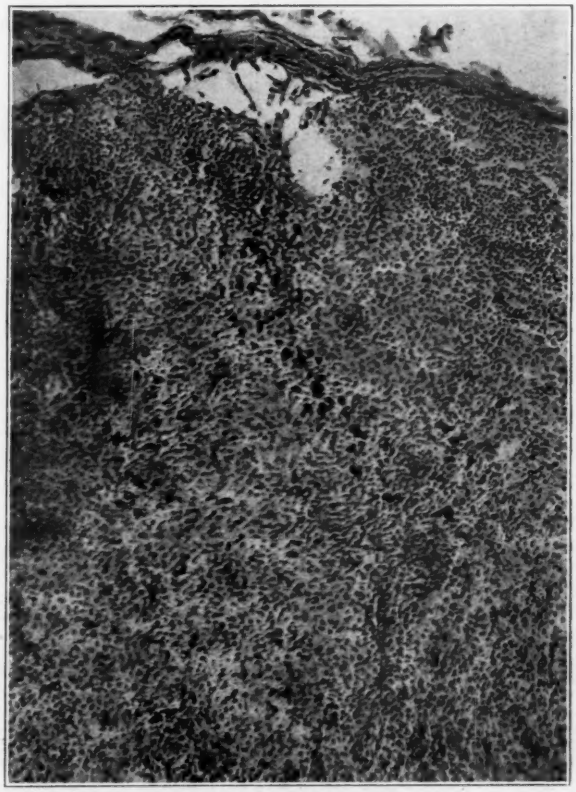

Fig. 5 (case 3).—Hyperplasia of reticular cells in the cortex of a lymph node. Many of these cells contain melanin. No lymph follicles are present. Hematoxylin and eosin; × 100.

were normal in number, but a few large forms were seen. Blood smears stained by the supravital method showed the structure of these cells to be more like the structure of the lymphocytic than that of the monocytic series."

Aspiration of the sternal marrow on the first day in the hospital showed normal marrow cells, the only abnormality being a slight increase in the number of eosinophils.

A clinical diagnosis of monocytic reticuloendotheliosis or Schilling type of monocytic leukemia was made.

On her second day in the hospital a biopsy of the skin of the left arm showed the epidermis to be the seat of hyperkeratinization, parakeratosis and acanthosis. The upper third of the dermis was infiltrated with many cells including lymphocytes and large mononuclear cells. Some of the latter had atypical deeply chromatic nuclei of irregular shape. Kingsley and reticulin stains revealed no cells of the granulocyte type and no increase in the amount of reticulin. Because of distinct nuclear pleomorphism of the cells in the dermis (fig. 8 *A*), the original diagnosis of chronic dermatitis was revised to lymphoblastoma "consistent with

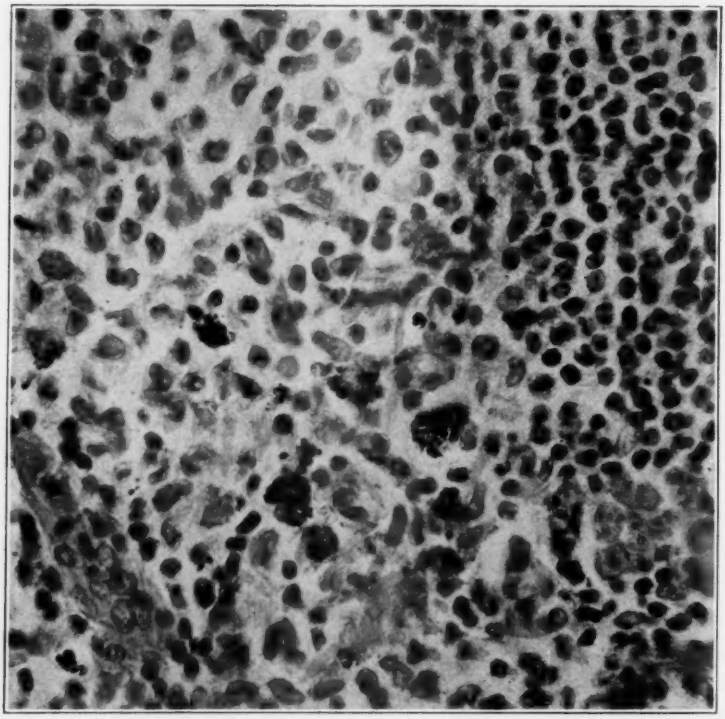

Fig. 6 (case 3).—Large reticular cells are present in the cortex of a lymph node; some of these contain melanin. Hematoxylin and eosin; × 660.

a diagnosis of monocytic leukemia." It should be noted that no eosinophils were present in the dermis.

On her seventh day in the hospital one of the lymph nodes in the left inguinal area was removed. The surgical specimen consisted of a lymph node 2.2 cm. in maximum measurement. Its capsule was intact, and its consistency and resistance to section were reduced. The bulging cross section was pinkish yellow. The microscopic features were those of lipomelanotic reticular hyperplasia and leukemic infiltration. There was moderate alteration in the normal architectural pattern. Lymph follicles were few in number and widely separated. Large mono-

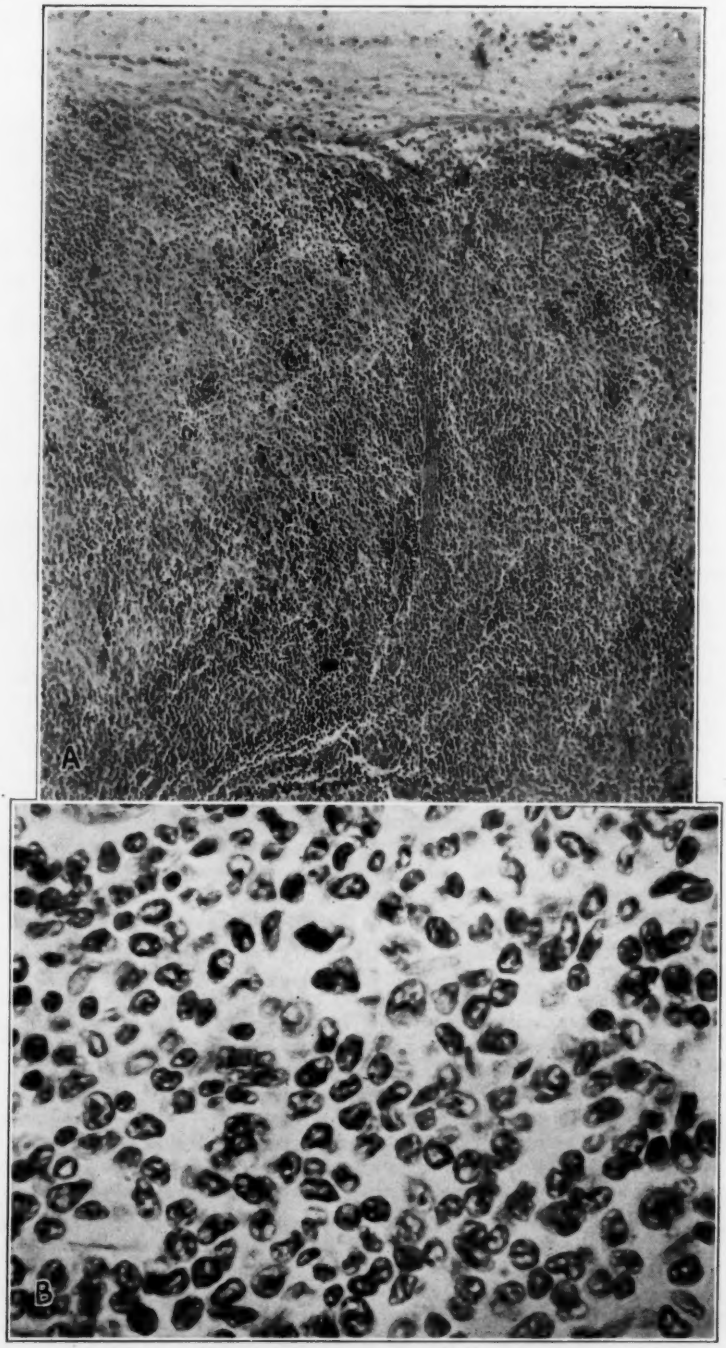

Fig. 7 (case 4).—*A*, hyperplasia of reticular cells in the cortex of the lymph node. No lymph follicles are present. Hematoxylin and eosin; × 100. *B*, cells of large size with indented nuclei (cells of monocyte series) are present in the medulla of a lymph node. Hematoxylin and eosin; × 850.

nuclear (reticular) cells with faintly eosinophilic cytoplasm were abundant throughout the cortex (fig. 7*A*). A considerable amount of sudanotropic material was present in the large reticular cells, but melanin was not abundant and eosinophils were few in number. On the first examination the presence of atypical cells was not noted. With more careful scrutiny, many cells of unusual type were noted, particularly in the medulla. These were large cells with indented nuclei of variable size and homogeneous, moderately eosinophilic nonvacuolated cytoplasm. (fig. 7*B*). Lymphocytes were scarce.

The patient was discharged on the sixteenth day in the hospital after having shown decided improvement.

She was again hospitalized on Sept. 29, 1945, because of "strangling attacks and shortness of breath." In February 1945 she noticed loss of hearing of the left ear. Subsequently she became excited, maniacal and hysterical. She was kept in a sanatorium for four weeks, during which time she had dyspnea without relation to exertion, position or meals, but her excitement decreased. After leaving the sanatorium she became more nervous and began taking sedatives and stimulants. On August 16, while sitting in a chair, she suddenly became dyspneic, excited and flushed. After this time such attacks became more pronounced and frequent. During the attacks she was flaccid and could not talk.

At the time of the second admission the urine contained albumin (2 plus) and 50 to 70 white blood cells and a few casts in the sediment. The red blood cell count was 4,190,000, with a hemoglobin content of 80 per cent (Sahli), and a white blood cell count of 10,500 (65 per cent neutrophils, 7 per cent lymphocytes, 3 per cent monocytes, 2 per cent eosinophils and 23 per cent atypical monocytoid cells).

Course in the Hospital.—The temperature varied between 37.3 and 38 C. (99 to 100.4 F.). Roentgenograms of the chest showed no enlargement of the lymph nodes and no change since the previous examination in January 1945. With roentgen ray treatment the superficial lymph nodes decreased moderately in size. The pruritus was controlled by means of massage with olive oil and mineral oil and sedation. The patient was discharged to a nursing home on the eighth day in the hospital. The clinical diagnosis was Schilling's monocytic leukemia, arteriosclerotic heart disease and attacks of anxiety hysteria.

She remained in the nursing home for the next nine months. Her condition gradually became worse, and she died on May 25, 1946.

The autopsy revealed monocytic leukosis (Schilling type), with involvement of the thymus, pericardium, lungs, liver (1,910 Gm.), spleen (700 Gm.), adrenals, kidneys, lymph nodes and bone marrow. The immediate cause of death was bilateral bronchopneumonia.

The microscopic changes in the involved organs were different from those in the skin and lymph nodes examined sixteen months prior to the patient's death. The large mononuclear cells showed more variation in size and shape, distinct nuclear pleomorphism and acidophilic homogeneous cytoplasm. Mononuclear cells containing sudanotropic material, melanin and eosinophils were not present.

CASE 5.—S. N., a white woman aged 64 years, was admitted to the hospital on April 26, 1945, with the complaint of "itchy skin." Her illness began in the winter of 1941, when her skin became red, rough and scaly. The condition gradually became worse up to the time of her hospitalization.

In the past she had always been "nervous and high strung." She had frequently been troubled with "nervous indigestion," and in 1937 she had had an attack of "mucous colitis." She had also noted moderate exertional dyspnea,

slight swelling of the legs, substernal pain, palpitation and nocturia. She had undergone thyroidectomy in 1942.

Physical examination at the time of admission revealed a temperature of 37.7 C. (99.8 F.), a pulse rate of 88, a respiratory rate of 22 and a blood pressure of 170 systolic and 70 diastolic. She was well developed and well nourished and appeared apprehensive but not seriously ill. The skin of the trunk and extremities was red and rough. The cutaneous changes were symmetrically distributed and were most pronounced on the lateral aspects of the extremities, where scaling and excoriations were particularly notable. The lymph nodes in the right and left axillary and inguinal areas were moderately enlarged, firm and nontender, The thorax was normal except for a slight increase in the anteroposterior diameter. The heart was not enlarged on percussion, but a systolic murmur was heard at the apex. All reflexes were markedly hyperactive.

Laboratory tests on the day of admission gave the following results: The urine was normal except for the presence of 10 to 15 white blood cells and occasional granular casts per high power field. The red blood cell count was 3,870,000, with a hemoglobin content of 82 per cent (Sahli), and the white blood cell count 10,150 (69 per cent neutrophils, 27 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils).

Course in the Hospital.—Additional laboratory examinations revealed fasting blood sugar contents of 79, 102 and 110 mg. per hundred cubic centimeters and curves for glucose tolerance like those of a patient with a slight degree of diabetes mellitus. The basal metabolic rate was + 5, and there was slight enlargement of the heart on roentgenologic examination. The white blood cell count varied between 8,800 and 14,300, with a differential count similar to that at the time of admission to the hospital except that there were many monocytes of the Schilling type.

On the fourth day in the hospital an elevated cutaneous nodule was excised. Microscopic examination revealed moderate hyperplasia of the epidermis, with moderate hyperkeratinization and appreciable acanthosis. In the deeper part of the dermis there were typical nevus cells, and in the upper part there were small and large mononuclear cells. The large mononuclear cells showed distinct abnormality of nuclei, but the changes were not considered to be sufficient in degree to warrant a positive diagnosis of leukemia.

On the eighth day in the hospital one of the lymph nodes in the right inguinal area was removed. The surgical specimen consisted of a lymph node with a diameter of 1.2 cm. Its consistency and its resistance to section were average. The cross section was pale pink. The microscopic sections showed a normal architectural pattern, with a few lymph follicles. Large reticular cells with abundant pale eosinophilic cytoplasm were numerous in the medulla and in the inner part of the cortex. Some of the reticular cells contained sudanotropic droplets, and in a few there was dark brown pigment that was soluble in hydrogen peroxide (fig. 8*B*). In addition there were many cells with indented nuclei suggestive of monocytes, particularly in the medulla.

While the patient was in the hospital her skin was kept oiled with coal tar, ammoniated mercury and petrolatum containing cod liver oil. She was discharged on the twenty-fifth day in the hospital slightly improved. The clinical diagnosis was Schilling's monocytic leukemia and diabetes mellitus.

Case 6.—J. B., a Negro of 52 years of age, was referred to the dispensary because of varicose veins of the legs. His history indicated that he had had varicose veins for ten years, an ulcer on the right leg for eight months and an ulcer of the left leg for two months. The ulcer on the right leg had healed on

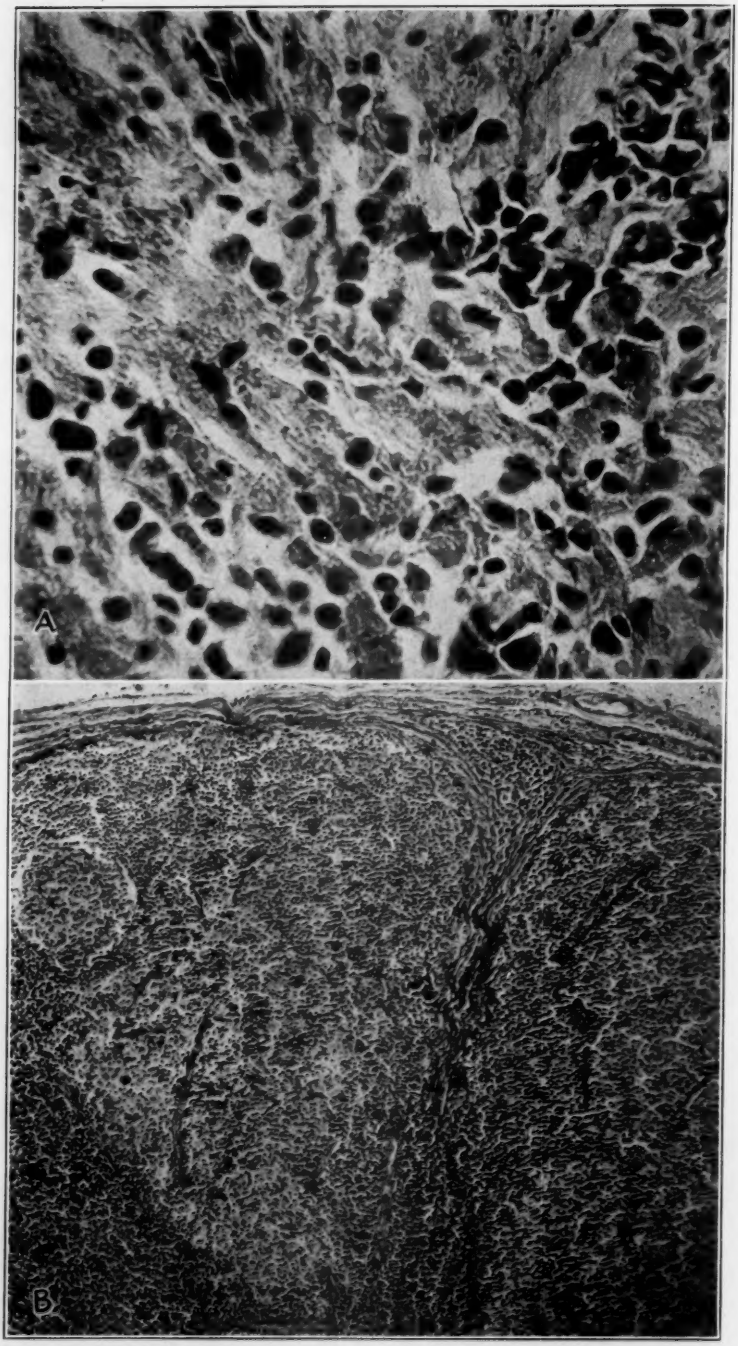

Fig. 8.—*A* (case 4), cells in the dermis show distinct variation in size and have large and irregularly shaped nuclei. The cellular infiltration is due to monocytic leukosis. Hematoxylin and eosin; × 660. *B* (case 5), increase of reticular cells and deposition of melanin in the periphery of a lymph node. One lymph follicle with a secondary center is present. Hematoxylin and eosin; × 100.

several occasions after periods of rest. Physical examination revealed an enlarged and tortuous right long saphenous vein, a patent deep venous system on the right, an ulcer measuring 3 inches (7.6 cm.) in diameter on the medial aspect of the right leg, palpable thrombosed veins of the left lesser saphenous system, a patent deep venous system on the left, an ulcer half an inch (1 cm.) in diameter over the left medial malleolus, moderately enlarged nontender inguinal lymph nodes and a small firm nodule medial to and below the right patella.

On Sept. 9, 1946, ligations of the saphenous veins were done high and low on the right side; the nodule below the right patella and a lymph node in the right inguinal area were removed. The nodule was cut into at the time of operation and contained clear colorless gelatinous material.

The surgical specimen included the cyst wall and lymph node. The former was made up of dense fibrous connective tissue in which there were a few lymphocytes and large mononuclear cells. The lymph node had a maximum measurement of 1.3 cm. It was average in consistency and sectioned with the usual resistance. The cross section was pale pink. Microscopic examination revealed focal fibrosis and normal lymph follicles. Reticular cells of large size with large amounts of faintly eosinophilic cytoplasm were present in moderately increased numbers in the medulla. A few of these cells contained sudanotropic droplets, and many contained brown pigment that was identified as melanin by its solubility in hydrogen peroxide. Eosinophils were few. The diagnosis was slight chronic inflammation of a cyst wall and slight lipomelanotic reticular hyperplasia of a lymph node.

The patient was last seen on Sept. 24, 1946, at which time the surgical wounds were well healed. The ulcers were cleaned and dressed. He did not return to the dispensary as instructed.

COMMENT

The cases recorded in this paper are illustrative of a distinct clinicopathologic entity which, although not generally recognized, is probably not uncommon. The clinical manifestations include dermatitis, usually with severe pruritus and enlargement of lymph nodes. The cutaneous lesions vary in degree and distribution. There is usually considerable erythema, scaling and excoriation. A typical exfoliative dermatitis may develop. The lymphadenopathy may be widespread but is in most instances particularly notable in the axillary and inguinal regions. The enlarged lymph nodes are chracteristically firm, discrete and nontender. Other manifestations of lymphoblastoma such as persistent leukocytosis, abnormal white cells in the circulating blood, anemia, and splenomegaly are absent in the uncomplicated cases.

Biopsies of skin reveal chronic dermatitis without a characteristic microscopic picture. The epidermis may be slightly thickened. The cellular infiltration of the dermis is made up of lymphocytes, large mononuclear cells and eosinophils. In some instances an occasional mononuclear cell contains melanin, but in none is there noteworthy cellular pleomorphism.

The lymph nodes are grossly enlarged and slightly softer than usual, and they have intact capsules. There is reduced resistance to section,

and they have bulging pale yellow cross sections. The yellow color is suggestive of the presence of fat, and rarely brown mottling due to melanin pigmentation is noted.[2] The microscopic picture of the lymph nodes is characteristic. The normal architectural pattern may be slightly altered, but it is never completely obscured. The predominant cell is the large mononuclear (reticular) cell with abundant faintly acidophilic cytoplasm that is frequently vacuolated. The cytoplasmic vacuolization is due to sudanotropic material, which is readily demonstrated with Sudan stains. These large cells are particularly conspicuous in the cortexes, where, when abundant, they alter the normal architectural pattern. The lymph follicles may be slightly enlarged, with distinct secondary centers, but they usually appear to be decreased in number because of wide separation by the large reticular cells in the cortical region. A varying number of large mononuclear cells contain granular dark brown pigment, which is identified as melanin by the lack of a reaction to potassium ferrocyanide and hydrochloric acid and by its solubility in hydrogen peroxide. Eosinophils, although not numerous, are always present. Plasma cells may be noted, but they are usually few in number. Fibrosis and giant cells are not part of the microscopic picture. Cellular pleomorphism is usually not striking. In this respect the case reported by Soloff,[2] in which there was appreciable cellular pleomorphism in the lymph node, is atypical.

The dermatitis is considered to be primary and the changes in the lymph nodes secondary. The inflammation of the skin causes hyperplasia of the draining lymph nodes. The scratching induced by pruritus probably brings about increased formation and liberation of melanin from cells of the epidermis. Such pigment would then be transported to regional lymph nodes and phagocytosed by reticular cells. Thus the amount of melanin pigmentation of the lymph node is dependent on the duration and severity of the pruritic dermatitis. The sudanotropic material in the reticular cells is probably secondary to excessive amounts of fat entering the cutaneous lymphatic vessels as a result of scratching and injury.

In normal lymph nodes or in those which are the seat of ordinary follicular or reticular hyperplasia, melanin and fat are usually absent or are present in exceedingly small amounts. That small amounts of melanin may be present in otherwise normal lymph nodes was demonstrated by Keye.[3] For comparison with the lymph nodes in the cases reported in this paper, forty lymph nodes which were the seat of reticular and follicular hyperplasia were examined and stained with Sudan

3. Keye, K. R.: Ueber die natürliche Abwanderung des Pigments aus der Haut in die Lymphdrüsen bei Pferden, Centralbl. f. allg. Path. u. path. Anat. **34**:57-60, 1923.

IV. In some there were a few reticular cells that contained sudanotropic droplets, but in none was the amount of sudanotropic material as great as in the lymph nodes which were the seat of lipomelanotic reticular hyperplasia.

The mechanism of development of lipomelanotic reticular hyperplasia of lymph nodes is such that it can theoretically occur in any condition of inflammation and itching of the skin. Thus the presence in lymph nodes of changes characteristic of lipomelanotic reticular hyperplasia does not of necessity preclude the concomitant existence of a lymphoblastoma. Thus in cases 4 and 5 the changes in the blood, skin and lymph nodes were consistent with a diagnosis of monocytic leukosis of Schilling type. It should be noted that in both instances the changes in superficial lymph nodes were those of lipomelanotic reticular hyperplasia as well as of monocytic leukemia. At the time of autopsy the microscopic changes in the thymus, liver, spleen, lymph nodes, kidneys and bone marrow in case 4 were different from those in lipomelanotic reticular hyperplasia. In these organs the large mononuclear cells showed considerable variations in size and shape, distinct nuclear pleomorphism and moderately acidophilic, homogeneous, nonvacuolated cytoplasm without sudanotropic droplets. None of the lymph nodes contained melanin or eosinophils. From an anatomic standpoint, therefore, the microscopic features of Schilling's monocytic leukosis and those of lipomelanotic reticular hyperplasia of lymph nodes are easily distinguished. Nevertheless, patients with the Schilling type of monocytic leukosis [4] usually have a relatively long course of illness, and cutaneous lesions with pruritus may develop. It is essential, therefore, that the possibility of the existence of this type of monocytic leukemia be kept in mind in the treatment of patients who have the clinicopathologic entity of pruritic dermatitis and lipomelanotic reticular hyperplasia of lymph nodes.

SUMMARY

Chronic dermatitis, particularly when accompanied with pruritus, may result in a characteristic type of hyperplasia of lymph nodes. The lymph nodes are usually moderately enlarged, discrete, firm and nontender. On gross examination they frequently have a yellow tinge and occasionally show dark brown mottling. The microscopic features include slight distortion of normal architectural pattern, severe hyperplasia of reticular cells, which contain melanin and sudanotropic droplets, and infiltration with eosinophils. The secondary centers of the lymph follicles are sometimes evident, but the notable proliferation of

4. Montgomery, H., and Watkins, C. H.: Monocytic Leukemia: Cutaneous Manifestations of the Naegeli and Schilling Types; Hemocytologic Differentiation, Arch. Int. Med. **60**:51-63 (July) 1937.

reticular cells is in the pulp of the lymph nodes. Six cases of dermatitis and this type of hyperplasia of lymph nodes are reported. In many instances, because of the prominence of the lymphadenopathy an incorrect clinical diagnosis of lymphoblastoma may be made. A diagnosis of lipomelanotic reticular hyperplasia of lymph nodes does not preclude the possibility of the concomitant existence of a lymphoblastoma. Thus in 2 of the cases reported in this paper there were changes in the blood and tissues that warranted the diagnosis of Schilling's monocytic leukosis. Lipomelanotic reticular hyperplasia of lymph nodes is a benign lesion that is secondary to chronic pruritic dermatitis. Although it may be associated with leukemia, Hodgkin's disease or lymphosarcoma it has no direct relationship to them.

ADENOMAS OF THE ADRENAL CORTEX

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ADENOMAS of the adrenal cortex are reported in 1.45 to 33 per cent of all autopsies,[1] and they have been considered to be of significance in hypertension and diabetes mellitus.[2] This study represents an attempt to determine the incidence of adenomas of the adrenal cortex and to ascertain whether they occur more often in patients with hypertensive cardiovascular disease, cardiac enlargement, diabetes mellitus or gonadal changes.

For this study, any roughly spherical nodule with a diameter greater than 3 mm. budding from an edge of the gland or into the medulla was considered to be an adenoma of the adrenal cortex. The tumors contained variable proportions of vacuolated and eosinophilic cells resembling those of the adrenal cortex. The histologic architecture, however, was distinctly different from that of normal adrenal cortex. None of the nodules showed evidence of malignant change. Detailed reports of cytologic and histologic characteristics have been made previously.[3]

OBSERVATIONS

Reports on 9,866 consecutive autopsies from January 1932 to March 1943 were examined. In the reports on 7,437 a gross and

From the Mallory Institute of Pathology, Boston City Hospital, Boston.

1. (*a*) Russi, S.; Blumenthal, H. T., and Gray, S. H.: Small Adenomas of the Adrenal Cortex in Hypertension and Diabetes, Arch. Int. Med. **76**:284-291 (Nov.-Dec.) 1945. (*b*) Goldzieher, M. A.: The Adrenal Glands in Health and Disease, Philadelphia, F. A. Davis Company, 1944, pp. 97-103.

2. Rinehart, J. F.; Williams, O. O., and Cappeller, W. S.: Adenomatous Hyperplasia of the Adrenal Cortex Associated with Essential Hypertension, Arch. Path. **32**:169-177 (Aug.) 1941. Russi and others.[1a]

3. (*a*) Moore, R. A.: A Textbook of Pathology, Philadelphia, W. B. Saunders Company, 1944, pp. 1068-1069. (*b*) Kaufmann, E.: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 2, pp. 1287-1288. (*c*) Broster, L. R., and others: The Adrenal Cortex and Intersexuality, London, Chapman & Hall, Ltd., 1938, pp. 163-164. (*d*) Grollman, A.: The Adrenals, Baltimore, Williams & Wilkins Company, 1936. (*e*) Russi and others,[1a] (*f*) Goldzieher.[1b]

microscopic description of the adrenal glands was recorded. Single or multiple adenomas of the adrenal cortex were noted in 216 of the 7,437 (2.86 per cent). The age and sex distribution is shown in table 1. The incidence was equal among males and females and low in the first three decades of life. A trend toward an increasing incidence in later years is suggested by the data, but beyond the fifth decade the differences are not statistically significant when compared with the total number of autopsies performed (table 2).

A study was made of the available clinical and pathologic data on the 100 most recent consecutive cases in which adenomas of the adrenal cortex were found. Twenty-five of the patients had hyper-

TABLE 1.—*Incidence of Adrenal Adenomas in 7,437 Autopsies (4,519 on Males, 2,918 on Females)*

1. Total number of adenomas: 216 (130 in males, 86 in females)
2. Percentage with adenomas: 2.86 (2.88 in males, 2.84 in females)
3. Percentage with adenomas by age groups:

Age range	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90
Total	0	0	0.5	1.9	2.4	2.8	4.9	3.5	6.8
Males	0	0	0.0	2.1	2.2	2.4	5.2	3.3	8.1
Females	0	0	0.9	1.6	2.7	3.5	4.3	3.8	5.4

TABLE 2.—*Age Distribution by Percentage in 7,437 Autopsies (4,519 on Males, 2,918 on Females) at the Mallory Institute of Pathology, Boston City Hospital*

Age range	0-10	10-20	20-30	30-40	40-50	50-60	60-70	70-80	80-90	90-100
Total	9.3	2.7	5.3	8.2	14.7	20.8	21.0	14.7	3.1	0.2
Males	8.7	2.4	4.1	7.3	15.4	22.4	21.3	15.6	2.7	0.1
Females	10.3	3.2	7.3	8.8	13.8	18.4	20.6	13.5	3.8	0.3

tensive cardiovascular disease, and 3 had diabetes mellitus. In 1,353 unselected consecutive autopsies performed in 1945 and 1946 the incidence of hypertensive cardiovascular disease was 14.6 per cent and that of diabetes mellitus was 3.4 per cent. Although the incidence of hypertensive cardiovascular disease is 10 per cent higher among the patients with adrenal adenomas, this is probably not significant because the 1,353 consecutive autopsies involved patients of all ages (one fourth under the age of 40) whereas the youngest patient with an adenoma of the adrenal cortex in the series of 100 studied was 42 years. Since hypertensive cardiovascular disease is most commonly encountered in patients past the age of 40, the incidence among the 100 cases probably reflects this variable. It is apparent that the incidence of diabetes mellitus was the same in the 100 cases in which there was adenoma of the adrenal cortex as in the 1,353 unselected autopsies.

In the series of 100 cases a weight above 350 Gm. was recorded for the heart in 51. Since such a weight, in the absence of valvular

disease, is considered in adults to be suggestive of hypertension,[1a] reports on 200 consecutive autopsies on patients above the age of 14 years, in which the heart had been weighed, were reviewed. In a total of 124 (62 per cent) the heart weighed over 350 Gm. These data fail to show an increased incidence of cardiac enlargement in patients with adenomas of the adrenal cortex.

There were 21 of the patients with adenomas of the adrenal cortex for whom microscopic pictures of the gonads were available for review. In 12 of these involutionary changes were found.[4] Inasmuch as changes of this nature are expected in approximately half of the patients in

TABLE 3.—*Incidence of Cardiac Involvement and Diabetes in Patients with Adrenal Adenomas as Compared with That in Unselected Autopsies*

A. Incidence of hypertensive cardiovascular disease and diabetes as diagnosed on combined clinical and pathologic evidence in 1,353 autopsies *

	Hypertensive Cardiovascular Disease	Diabetes
Total number	198	46
Percentage	14.6	3.4

B. Incidence of hypertensive cardiovascular disease, diabetes and increased weight of the heart (greater than 350 Gm.) in one hundred patients with adrenal adenomas †

	Hypertensive Cardiovascular Disease	Diabetes	Heart Weight Above 350 Gm.
Total number	25	3	51
Percentage	25	3	. 51

C. Incidence of increased weight of the heart (greater than 350 Gm.) in two hundred autopsies on adults
Total number, 124; percentage, 62

* These were unselected consecutive autopsies on a group which included patients in the first four decades of life.
†The age of the patients ranged from 42 to 89 years.

this age range, no relationship between gonadal changes and adenomas of the adrenal cortex is suggested.

COMMENT

The literature concerning adenomas of the adrenal cortex is difficult to interpret accurately because of differences in criteria in the classification of enlargement of the adrenal cortex. (For a review of adrenal hypertrophy see Tepperman, Engel and Long.[5]) Moore [3a] stated: "The frequency of local hyperplasia and adenoma of the adrenal cortex is in indirect ratio to the exactness of criteria and examination. Most adrenals contain some type of spherical mass. Grossly demonstrable

4. The criteria used were (1) the amount of fibrosis, (2) the follicular or spermatogenic activity, (3) the thickness of the lamina propria and the number of Leydig cells in the testes and (4) the appearance of corpora lutea in the ovaries.

5. Tepperman, J. F.; Engel, F. L., and Long, C. N. H.: A Review of Adrenal Cortical Hypertrophy, Endocrinology **32**:373-402 (May) 1943.

nodules are present in about 10 per cent of all adults." Torgersen [6] suggested that medullary nodules are no more than an indication of the fact that the cortical-medullar margin is extremely irregular and folded and that the "islands" actually are "peninsulas" which seem isolated because of the angle in which the section has been cut. Goldzieher [1b] asserted that adenomatous nodules are observed in about 33 per cent of all adults regardless of age or sex. Grollman [3d] reported that cortical hyperplasia may occur either in the form of diffuse hyperplasia or as circumscribed nodules ranging in size from microscopic islets of tissue to the size of a hen's egg and that it is an incidental finding in about a third of all autopsies. Russi, Blumenthal and Gray [1a] reported the presence of small adenomas of the adrenal cortex in 1.45 per cent of 9,000 consecutive autopsies.

This study does not include so-called diffuse hyperplasia or "true" cortical adenomas (with complete capsule) as defined by Ewing.[7] The terms adenomatous hyperplasia, focal adenomas and cortical adenomas are used by various authors in their discussions of the pathologic findings described. A surgical study such as that of Castleman and Smithwick [8] is concerned only with adrenal tumors which are observable grossly. The observed incidence of 2.86 per cent confirms the belief that adenomas of the adrenal cortex are not unusual in adults of either sex. The age distribution suggests an increasing incidence with advancing years.

Russi, Blumenthal and Gray [1a] concluded that "hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general autopsy group." Rinehart, Williams and Cappeller [2] have stated: "The correlation of hyperplasia of the adrenal cortex with essential hypertension is almost as definite as that of hyperplasia of the thyroid gland with exophthalmic goiter." Dempsey,[9] reviewing autopsy material similar to that on which Rinehart and his colleagues based their conclusions, found no significant difference in the weight or structure of the adrenals of those with hypertension and of those without it. Moore [3a] has written that there is no established relation between focal hyperplasia and adenoma of the adrenal cortex and hypertension.

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6. Torgersen, O.: Histological Studies on the Normal and the Irradiated Suprarenal Gland in Rabbits, Oslo, I Kommisjen Los Jacob Dyburad, 1940.

7. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1941, pp. 830-831.

8. Castleman, B., and Smithwick, R. H.: The Relation of Vascular Disease to the Hypertensive State Based on Study of Renal Biopsies from One Hundred Hypertensive Patients, J. A. M. A. **121**:1256-1261 (April 17) 1943.

9. Dempsey, W. S.: The Adrenal Cortex in Essential Hypertension, Arch. Path. **34**:1031-1034 (Dec.) 1942.

Selye has presented evidence [10] of a relationship between adrenal function and hypertension. However, the data presented here fail to indicate that the morphologic abnormality under study is related to or indicative of pathologic changes producing hypertensive cardiovascular disease. The incidence of diabetes mellitus and cardiac enlargement was essentially the same in our series of patients with adenomas of the adrenal cortex as in the control groups.

Broster [3c] has suggested that the focal hyperplasias of the adrenals, prostate and breast are related to involutionary processes of the gonads. Woolley, Fekete and Little [11] reported that gonadectomy in a selected strain of mice led almost invariably to adrenal neoplasms. Adenomas of the adrenal cortex could possibly constitute an adrenal compensatory mechanism for waning or absent gonadal steroid output. If this premise were true, cellular or architectural changes in the gonads would be helpful evidence. However, no gonadal changes were found which were greater than those observed in routine autopsies on patients of a similar age group.

SUMMARY

Adenomas of the adrenal cortex larger than 3.0 mm. were encountered in 216 (2.86 per cent) of 7,437 consecutive autopsies in which the adrenals were observed. The incidence was the same in males as in females. An adenoma was found in only 4 patients under the age of 40 years. A progressively greater incidence with increasing age was noted.

There was no significant difference in the incidence of hypertensive cardiovascular disease, cardiac enlargement, diabetes mellitus or gonadal changes in patients with adenomas of the adrenal cortex as compared with that in patients without such tumors.

Evans Memorial Hospital.
Stanford-Lane Hospital.

10. Selye, H.: The General Adaptation Syndrome and the Diseases of Adaptation, J. Clin. Endocrinol. **6**:117-230 (Feb.) 1946.

11. Woolley, G. W.; Fekete, E., and Little, C. C.: Gonadectomy and Adrenal Neoplasms, Science **97**:291 (March 26) 1943.

METABOLIC STUDIES IN DIABETIC ACIDOSIS

II. The Effect of the Administration of Sodium Phosphate

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IT IS now well recognized that the phosphate cycle constitutes the mechanism whereby energy resulting from oxidation is rendered available to living cells.[1] A notable rise in the plasma level and urinary excretion of phosphorus has been found in diabetic acidosis.[2] This apparently causes a significant depletion of phosphorus stores in the body, as shown by the response to insulin. The plasma and urinary phosphorus levels fall precipitously and remain subnormal for as long as a week after institution of insulin therapy.[2b]

The fact that death may occur in circulatory collapse after abolition of ketosis, restoration of a normal blood sugar level and replacement of apparently adequate amounts of water and sodium chloride raises

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Read by title at the meeting of the American Society for Clinical Investigation, May 1946.

From the Department of Medicine of Wayne University College of Medicine and the City of Detroit Receiving Hospital.

1. Lipmann, F.: Metabolic Generation and Utilization of Phosphate Bond Energy, in Nord, F. F., and Werkman, C. H.: Advances in Enzymology, New York, Interscience Publishers, Inc., 1941, vol. 1, p. 91.

2. (*a*) Atchley, D. W.; Loeb, R. F.; Richards, D. W., Jr.; Benedict, E. M., and Driscoll, M. E.: On Diabetic Acidosis: A Detailed Study of Electrolyte Balances Following the Withdrawal and Re-Establishment of Insulin Therapy, J. Clin. Investigation **12**:297, 1933. (*b*) Guest, O. M., and Rapoport, S.: Role of Acid Soluble Phosphorus Compounds in Red Blood Cells in Experimental Rickets, Renal Insufficiency, Pyloric Obstruction, Gastroenteritis, Ammonium Chloride Acidosis and Diabetic Acidosis, Am. J. Dis. Child. **58**:1072 (Nov.) 1939. (*c*) Harrop, G. A., and Benedict, E. M.: Participation of Inorganic Substances in Carbohydrate Metabolism, J. Biol. Chem. **59**:687, 1924. (*d*) Kaplan, N. O.; Franks, M., and Friedgood, C. E.: Metabolism in Diabetic Coma Produced by Alloxan, Science **102**:447, 1945.

the question of the clinical importance of deficiency of other elements, notably phosphorus and potassium. One of the objectives of the present study was to determine the clinical efficacy of intravenously administered sodium phosphate as an adjuvant to the therapy of diabetic acidosis.

The method of study and the clinical material were described in detail in a preceding paper. The results are presented in tables 1 to 12 inclusive of the preceding paper and in tables 1 and 2 of this communication. The patients receiving phosphorus also were treated with large amounts of dextrose. Therefore, for the most part the dextrose-treated patients serve as the controls.

RESULTS

Plasma Inorganic Phosphorus Levels on the Patients' Admission to the Hospital.—The plasma inorganic phosphorus level was definitely elevated in 28 patients prior to treatment, ranging from 4.23 to 17.20 mg. per hundred cubic centimeters and averaging 7.88 mg. The level could not be correlated with the blood sugar content, the degree of acidosis, or the clinical state as measured by the blood pressure, mental state or complications.

Effect of Insulin on Plasma and Urinary Phosphorus Levels.—The plasma inorganic phosphorus level fell precipitously during the first four to five hours in all but 2 cases. By the end of the first period it was below 1 mg. per hundred cubic centimeters in 5 cases, between 1 and 2 mg. in 12 cases and between 2 and 3 mg. in 6 cases (table 1). In cases 11 and 12 the level did not change significantly during the first four hours of treatment despite apparent glucose retention and combustion but fell subsequently to below 1 mg. by the end of ten hours in the former and after twenty-four hours in the latter. The lowest level during the first day of treatment was less than 1 mg. per hundred cubic centimeters in 10 cases and between 1 and 2 mg. in the remaining 18.[3] From a comparison of the patients treated with dextrose during the first four hours and those not so treated, it is evident that the early administration did not accelerate the fall in plasma inorganic phosphorus or the rate of its urinary excretion. As a matter of fact, the decrement in plasma inorganic phosphorus during the first period was slightly greater and more precipitous in the group receiving only insulin and sodium chloride than in the group receiving supplementary dextrose. This may be attributable to the poorer clinical and metabolic state of the dextrose-treated patients.

The striking fall in the level of plasma inorganic phosphorus cannot be accounted for by excretion through the urine. This is illustrated

3. These figures include some interval determinations not shown in the table.

TABLE 1.—*Phosphorus Metabolism.*

Group	Case	Plasma Phosphorus, Mg./100 Cc. Period: Admission	1	2	3		4	Urine Phosphorus, Mg. per Hr. Period: 1	2	3	4	24 Hour Urinary Phosphorus: Total Mg.	Mg. per Hr.	Urinary Phosphorus in Periods 2, 3 and 4: Total Mg.		Mg. per Hr.
Saline	1	7.56	2.77	1.05	2.84		0.99	21.3	5.1	5.2	6.7	200.9	8.4	115.7		5.8
	2	7.68	1.53	2.43	1.69		1.85	52.2	15.3	19.7	4.9	533.3	22.2	246.0		13.3
	3	10.12	1.21	0.83	0.26		2.56	104.0	7.6	1.9	4.6	511.4	21.3	95.4		4.8
	4	9.60	2.44	2.44	1.65		0.88	158.2	82.3	48.3	10.1	1,649.0	68.6	700.0		38.8
	5	8.80	1.08	1.38	1.69		2.75	40.1	2.8	5.8	4.8	276.1	11.5	95.6		4.9
	6	8.37	1.76	—	—		—	51.8	—	—	—	—	—	—		—
	7	10.03	1.65	1.00	1.29		1.98	64.6	15.6	17.6	—	594.0	24.7	206.0		11.4
Average		8.88	1.78	1.52	1.57		1.84	70.3	21.5	16.4	6.2	627.4	26.1	243.1		13.2
Dextrose	8	17.20	4.26	1.76	1.22		1.80	0	0	15.9	3.2	—	—	—		—
	9	4.28	1.60	0.16	0.80		0.44	11.3	6.9	4.3	3.7	150.7	6.3	85.8		4.7
	10	10.04	5.24	0.96	0.46		—	91.8	67.4	11.2	—	—	—	—		—
	11	4.23	3.34	0.99	1.43		1.40	34.5	13.7	3.8	3.8	271.3	11.3	133.3		6.7
	12	8.14	8.51	5.17	3.60		0.54	29.3	203.8	30.4	48.0	1,550.0	64.9	1,442.0		72.1
	13	5.75	0.83	0.43	0.40		—	91.1	1.4	0.2	—	—	—	—		—
	14	7.41	1.06	1.06	1.43		1.48	13.7	0	0	0	82.0	3.5	0		0
	15	11.60	2.28	0.95	1.88		2.20	—	—	—	—	—	—	—		—
	16	4.50	0.32	0.14	0.08		1.08	35.3	3.8	3.9	1.8	172.5	7.2	66.5		3.2
	17	5.70	0.49	0.06	0.06		—	164.4	99.0	—	—	—	—	—		—
	18	7.65	1.46	1.17	1.69		1.48	92.8	19.7	6.1	5.3	540.9	22.5	169.9		8.5
Average		7.86	2.67	1.17	1.19		1.30	56.4	41.6	7.6	9.4	462.7	19.3	316.2		19.0
Receiving 1,319 Mg. of Phosphorus																
Phosphorus	19*	5.98	2.34	4.77	....	(0.82)†	1.80	59.6	36.4	9.6	8.8	404.9	16.9	216.9		10.4
	20*	6.30	1.14	5.27	....	(1.87)†	—	58.4	136.0	—	—	—	—	—	Aver-	—
	21	8.26	1.01	3.70	0.69		1.69	47.2	92.5	17.3	5.4	599.7	29.2	305.9	age	21.5
	22	5.12	2.54	5.36	2.48	(1.44)†	1.60	27.4	44.7	35.6	21.1	666.1	27.7	574.8	376.0	27.8
	23	10.10	4.60	9.64	2.60	(1.65)†	2.26	66.3	74.2	36.4	3.9	638.3	26.6	406.9		19.8
Receiving 2,638 Mg. of Phosphorus																
	24	7.20	0.94	5.30	2.07		—	40.1	19.0	18.2	4.7	402.6	19.7	174.6		11.8
	25	9.49	0.80	5.85	3.92		3.76	30.3	58.3	42.0	24.8	877.1	36.3	620.4	Aver-	40.0
	26	7.15	1.29	6.00	2.76	(2.24)†	—	45.0	87.1	36.8	—	—	—	—	age	—
	27	6.20	1.73	7.46	1.37		1.67	71.7	—	122.2	35.7	1,181.8	49.2	895.0	721.6	44.8
	28	6.03	2.88	10.50	2.85	(1.09)†	2.58	41.7	173.5	111.2	30.3	1,432.4	59.7	1,196.4		65.3
Average		7.18	1.93	6.39	2.34		2.34	48.8	80.2	47.7	16.8	775.4	33.2	548.8		30.0

* Plasma phosphorus was not determined at the end of the third period.
† Figures indicate the lowest values in the third period.

by the patient in case 8, who was in complete anuria for the first eight hours, during which the level fell from 17.2 to 1.76 mg. per hundred cubic centimeters. It was also borne out by quantitative determinations of urinary phosphorus in the remaining cases.

Although there is no close agreement in the literature as to normal values for phosphorus excretion in nondiabetic patients or in those with controlled diabetes, the range is probably from 12.5 to 64 mg. per hour, with a mean of approximately 50 mg.[4] Urinary phosphorus excretion is known to be high in patients with uncontrolled diabetes [5] and was presumably increased in our cases prior to treatment. Urinary output of phosphorus fell within the normal range during the first four hours in 19 of 27 cases. In cases in which no supplementary phosphate was administered, the urinary level was invariably normal or subnormal after the ninth hour of treatment and was extremely low after the sixteenth hour in all but 1. Phosphorus excretion remained subnormal for as long as five days in such cases.

The Fate of Injected Phosphate.—Since previous studies and the foregoing data suggested that a deficiency of readily available phosphorus might exist in diabetic coma, buffered sodium phosphate solution [6] was given intravenously in 10 cases at a time when the plasma inorganic phosphorus was known to be low. The first 5 patients received 500 cc. of sodium phosphate solution containing 1,319 mg. of phosphorus. The injection was begun on an average of 3.95 hours after the patient came under treatment and was completed in an average period of 1.18 hours. The mean plasma inorganic phosphorus level at the end of the injection, 5.75 mg. per hundred cubic centimeters, was 3.42 mg. higher than the mean preinjection level of 2.33 mg. per hundred cubic centimeters. During the next few hours, a rather prompt return to normal or subnormal values took place. The rise in plasma inorganic phosphorus was relatively small in comparison with the fivefold to sixfold increase after similar doses in normal

4. Blatherwick, N. R.; Bell, M., and Hill, E.: Some Effects of Insulin on the Carbohydrate and Phosphorus Metabolism of Normal Individuals, J. Biol. Chem. **61**:241, 1924. Fiske, C. H.: Inorganic Phosphorus and Acid Excretion in the Post-Absorptive Period, ibid. **49**:171, 1921. Reiser, R.: Phosphorus Changes During the Absorption of Oil and Glucose, ibid. **135**:303, 1940. Robertson, J. D.: Calcium and Phosphorus Excretion in Thyrotoxicosis and Myxoedema, Lancet **1**:672, 1942. Sherman, H. C.: Phosphorus Requirements in Man, J. Biol. Chem. **40**:173, 1920. Walker, B. S.: Normal Relationships of Blood and Urine Phosphorus, J. Lab. & Clin. Med. **17**:347, 1931. Harrop and Benedict.[2c]

5. Atchley and others.[2a] Guest and Rapoport.[2b] Harrop and Benedict.[2c]

6. This was prepared according to the method of Ollayos and Winkler,[7] i. e., 12.33 Gm. of $NA_2H\ PO_4.\ 12H_2O$ and 1.12 Gm. of $NA\ H_2PO_4.H_2O$ were dissolved in distilled water and the solution sterilized by boiling for thirty minutes. It was then made to volume (500 cc.) and the p_H checked.

persons.[7] The urinary phosphorous level increased during the course of the injection but became normal shortly afterward and remained so for the rest of the twenty-four hours.

The total phosphorus excretion for the second, third and fourth periods in these first 5 patients averaged 376 mg. and was only 59.8 mg. greater than the average phosphorus output of the dextrose group. Since this output of 59.8 mg. in excess of that of the controls represents only 5 per cent of the 1,319 mg. administered, it would appear that 95 per cent of the injected phosphorus was retained.

Since the retention of almost 1,319 mg. of phosphorus failed to prevent subsequent hypophosphatemia, a larger dose was thought to be indicated. The second 5 patients were therefore given 2,638 mg. of phosphorus in 1,000 cc. of solution by slow intravenous injection

TABLE 2.—*Average Retention of Administered Phosphorus (P) from the Beginning of Injection to the End of the First Twenty-Four Hours (Periods 2, 3 and 4)*

Cases	(A) Administered P, Mg.	(B) P Excreted by Phosphate-Treated Patients	(C) P Excreted by Controls	(D=B—C) Excretion of Administered P,* Mg.	(E=A—D) Retention of Administered P †	(F=E÷A) Per Cent Retention ‡
5 cases in which 1,319 mg. of P was received	1,319	376	316	60	1,259	95
5 cases in which 1,319 mg. of P was received	2,638	722	316	406	2,232	85
Average of 10 cases	1,979	548	316	232	1,747	88

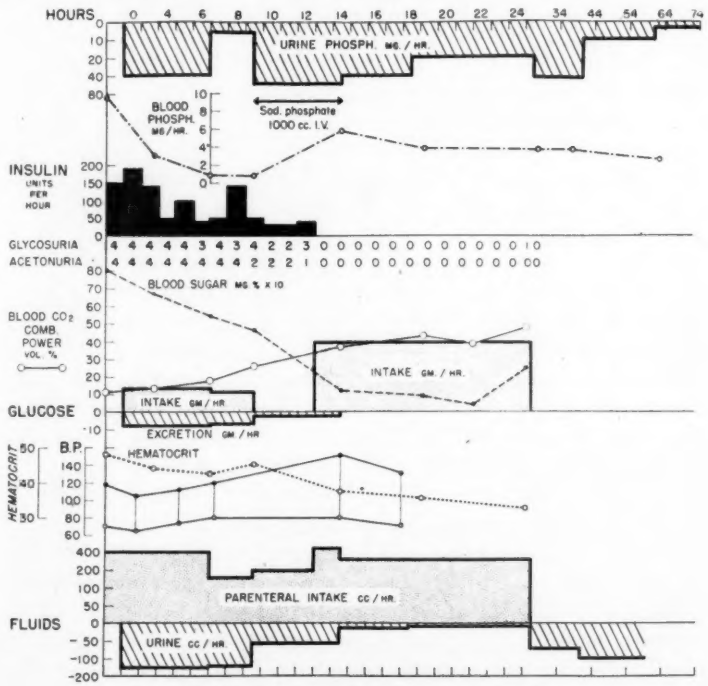
* Excretion of administered P = P excreted by phosphate-treated patients minus P excreted by controls.
† Retention of administered P = administered P minus excretion of administered P.
‡ Per cent retention = retention of administered P ÷ administered P.

over an average period of three and three-quarters hours. Doubling the dosage caused a greater rise in plasma inorganic phosphorus (5.49 mg. per hundred cubic centimeters as compared with 3.42 mg.) and a larger urinary output (721.6 mg. total for periods 2, 3 and 4 as compared with 376.0 mg.). Nevertheless, the plasma inorganic phosphorus subsequently fell to subnormal levels in 4 of these 5 patients, and hourly urinary excretion dropped below 50 mg. by the fourth period in all 5 receiving the larger dose. Furthermore, the apparent phosphorus retention at the end of twenty-four hours (calculated as before, with the dextrose group serving as controls) averaged 2,232.6 mg., or 85 per cent of the injected phosphorus. Thus the phosphate deficit in diabetic coma may not be corrected by administration of as much as 2,638 mg. of phosphorus.

7. Ollayos, R., and Winkler, A. W.: Urinary Excretion and Serum Concentration of Phosphate in Man, J. Clin. Investigation **22**:147, 1943.

The effect of the injection of 1,000 cc. of sodium phosphate on blood and urinary phosphorus, carbohydrate metabolism and acidosis is illustrated graphically in the accompanying figure, which depicts the course in case 25.

Phosphorus retention was demonstrable for several days after recovery from diabetic coma. When urinary loss in the phosphate group is corrected with that in the dextrose control group, the apparent retention of the injected phosphorus averaged 88 per cent in 8 cases at the end of twenty-four hours and 57 per cent in 5 cases at the end



Results of injection of sodium phosphate in case 25.

of forty hours. Four of the phosphate group were followed for longer periods, and data were obtained on the time required for the total urinary output of phosphorus, as measured from the start of the intravenous injection, to exceed the amount administered in this injection. More than seventy-two hours were required in 3 cases, more than ninety-six hours in 2 and more than one hundred and twenty hours in 1. Since the patients received considerable supplementary phosphorus through regular diabetic diets instituted after the first twenty-four to forty-eight hours, it is evident that phosphorus excretion was

subnormal for several days and that phosphorus was being stored in the tissues.

Effect of Sodium Phosphate on Carbohydrate Metabolism.—At the end of the second period, the average blood sugar content in the patients who had just received sodium phosphate was 351 mg. per hundred cubic centimeters and was thus closely comparable to the average level of 367 mg. in the dextrose control group. Thereafter the blood sugar level fell more rapidly in the phosphate group than in the dextrose group, as shown by average levels of 285 mg. in the former and 334 mg. in the latter at the end of the third period and average values of 129 and 273 mg. respectively at the end of the fourth period (table 4 in the previous paper). The superior control of carbohydrate metabolism in the phosphate group during the third and fourth periods cannot be explained by differences in insulin and dextrose intake during these periods, since the differential was in favor of the dextrose controls. Thus the average intake of dextrose during the third and fourth periods was 5 Gm. per hour more in the phosphate group (table 5 in the previous paper) and the average insulin dose 6.5 units per hour less in the phosphate group than in the dextrose control group (table 4 in the previous paper). These figures suggest that the partial correction of the phosphorus deficit accomplished through the administration of sodium phosphate had a favorable effect on carbohydrate metabolism. However, the data do not justify a positive conclusion because of the relatively small number of cases and because of a possible advantage which the phosphate group might have derived through the larger doses of insulin in the first period and the lower intake of dextrose during the first two periods.

Effect of Sodium Phosphate on Acidosis.—The degree of acidosis on admission of the patients to the hospital was greatest in the phosphate group and least in the saline group, as indicated by the clinical gradation of depression of consciousness, which averaged 3.1 for the phosphate group, 2.5 for the dextrose group and 2.0 for the saline group (table 1 in the previous paper), and by the carbon dioxide–combining power, which averaged 11.7, 14.0 and 16.1 volumes per cent respectively for the three groups (table 4 in the previous paper). Nevertheless the average time required for the disappearance of acetone from the urine was almost the same for the three groups. Return of consciousness was much more rapid during the administration of sodium phosphate than during a parallel period in the dextrose and saline controls. This will be elaborated on in the discussion of the clinical effects of sodium phosphate.

In order to ascertain the immediate effects of the administration of sodium phosphate on the carbon dioxide–combining power, all patients for whom the latter had been determined just before and

directly after the injection of the sodium phosphate were compared with the saline and dextrose controls, for whom the carbon dioxide–combining power had been obtained at the end of both the first and the second periods.[8] Among the 8 phosphate cases the carbon dioxide-combining power averaged 20 volumes per cent just before the start of injection of sodium phosphate and 30.2 volumes per cent after completion of the injection 2.75 hours later. Among the 14 control cases the carbon dioxide–combining power averaged 22.6 volumes per cent at the end of period 1 and 27 volumes per cent at the end of period 2, 4.04 hours later. Thus the average rise in the carbon dioxide–combining power during administration of sodium phosphate was 3.71 volumes per cent per hour, whereas the rise in the control cases during a comparable period was 1.09 volumes. The more rapid rise in the phosphate group may be due in part to a greater intake of sodium, since the total intake averaged 1.48 Gm. per hour in the phosphate cases during period 2 and 1.15 Gm. per hour in the controls during the same period. The difference in total hourly intake of sodium will not fully account for the greater rise of carbon dioxide–combining power and suggests that the sodium in the form of phosphate is better utilized for combating acidosis than the sodium ion in the form of sodium chloride, which was given to the controls. This might be anticipated from the fact that chloride remains almost entirely in the extracellular space in combination with sodium[9] whereas phosphate ion rapidly enters the cell,[10] leaving sodium behind to increase the alkaline reserve.

Effects of Phosphate on Water and Chloride Balance.—The data are difficult to interpret because of the variability in the cardiovascular status and the lack of information on blood volume, extracellular space and sodium and potassium output. Nevertheless, certain observations are noteworthy. Retention of water during the second, third and fourth periods—expressed in terms of either the total volume or the percentage of intake retained—was greatest in the phosphate group and least in the dextrose group. The phosphate group retained a total of 4,826 cc., or 71 per cent of the intake, during these periods, the saline group a total of 3,694 cc., or 69 per cent of the intake, and the dextrose

8. The data on cases 3, 6, 18 and 23 were eliminated because determinations of carbon dioxide–combining power were not available at both the beginning and the end of the period. The data on case 2 were also eliminated because the carbon dioxide–combining power had been raised at the beginning of the period to 63 volumes per cent by an infusion of sodium bicarbonate.

9. Peters, J. P.: Body Water, Springfield, Ill., Charles C Thomas, Publisher, 1935, p. 132.

10. Hevesy, G.: Application of Radioactive Indicators in Biology, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1941, vol. 9, p. 641.

group a total of 3,498 cc., or 50 per cent of the intake. In the interpretation of these figures, it is necessary to take into consideration the sodium intake, which favors water retention, and the glucose output, which promotes diuresis. The average intake of sodium ion for the second, third and fourth periods was 8.30 Gm. in the phosphate group, 6.43 Gm. in the saline group and 11.75 Gm. in the dextrose group. Total glucose outputs during the same interval were 70.9 Gm., 38.4 Gm. and 159.3 Gm. for the three groups respectively. In a comparison of the phosphate and dextrose groups, it is seen that the higher intake of sodium ion favored water retention in the latter, whereas the greater glucose output predisposed to diuresis. Similarly, the higher sodium intake in the phosphate group than in the saline group favored water retention in the former, while the greater glycosuria had the opposite effect.

The average value for the hematocrit reading on admission to the hospital was almost the same in the three groups, amounting to 54.1 per cent in the phosphate group and 54.7 per cent in both the saline and the dextrose controls (table 8 in the previous paper). The level at the end of the first period was likewise comparable, as shown by the figures of 42.6, 42.9 and 45.6 per cent for the three groups respectively. Thereafter the values for the hematocrit reading differed in the phosphate and control groups. Successive readings over a twenty hour period following the beginning of sodium phosphate injection revealed a progressive hemodilution, as shown by a drop from 42.6 to 36.6 per cent. Meanwhile the value was maintained at a plateau in the saline controls and was more irregular in the dextrose group, with a slight drop in the last specimen. The greater and more prolonged hemodilution in the phosphate group than in the control group suggests that phosphate administration may have aided in the retention of water in the vascular tree.

The plasma chloride was maintained at a higher and more constant level during the second, third and fourth periods in the phosphate group than in the saline or dextrose controls in spite of a lower chloride intake in the former during these periods (table 9 in the previous paper). This may be due to the release of chloride from the red cells as a result of more rapid restoration of organic phosphates in the cells when phosphate is given.

Clinical Effect of Administration of Sodium Phosphate.—No toxic manifestations were observed with either the 500 cc. or the 1,000 cc. dose of sodium phosphate solution. There was no evidence of latent or manifest tetany in any case. The serum calcium content was determined in a few cases, and no significant depression was revealed.

In the investigation of 71 successive cases of diabetic coma (table 12 in the previous paper), we found only one fatality among patients with

a severity index[11] below 30 per cent and no recovery among those with a severity index over 60 per cent. The outcome in the patients with a 30 to 60 per cent range was influenced by the therapeutic regimen. The poorest results were obtained in patients to whom dextrose was administered early. Of 18 such patients with an average severity index of 44 per cent, 12 (or 67 per cent) died. Among 11 patients who received dextrose early and sodium phosphate subsequently the severity index was 44 per cent and the actual death rate 27 per cent. Among 7 patients for whom administration of dextrose was postponed until the blood sugar level reached normal the severity index was 38 per cent and the fatality rate 42 per cent. Thus the administration of sodium phosphate seems to have modified the deleterious effect of early dextrose administration. Whether the use of sodium phosphate in cases in which dextrose is withheld until the blood sugar level falls to normal would further reduce the fatality rate remains to be determined in later work.

The most striking clinical effect was the improvement in mental state which seemed to coincide with the administration of sodium phosphate. The 3 patients who were unconscious at the start of the injection regained consciousness during its course. On the other hand, only 1 of the 5 controls regained consciousness during a comparable period. The improvement in mental state is further reflected in the greater over-all rise in the level of consciousness during the second period in the phosphate group than in the saline or dextrose controls. We have since observed this phenomenon of return of consciousness with administration of phosphate in patients who subsequently lapsed into coma and died.

A rise in systolic blood pressure was a fairly constant phenomenon, occurring in 9 of 10 cases, but the diastolic pressure varied only slightly. It was hoped that sodium phosphate might have a specific effect in shock associated with diabetic coma. However, in case 19 administration of 500 cc. of sodium phosphate failed to check a falling blood pressure. Because of approaching shock levels at the end of phosphate injection, 500 cc. of plasma was given, after which there was a distinct rise of blood pressure and shock was averted.

COMMENT

Since insulin is intimately concerned with the phosphorylation of glucose,[12] which is the necessary initial step for oxidation or storage

11. Collen, M. F.: Mortality in Diabetic Coma, Arch. Int. Med. **70**:347 (Sept.) 1942.

12. Price, W. H.; Cori, C. F., and Colowick, S. P.: The Effect of Anterior Pituitary Extract and of Insulin on the Hexokinase Reaction, J. Biol. Chem. **160**: 633, 1945.

as glycogen, lack of insulin should lead to an accumulation of inorganic phosphate and unphosphorylated glucose. An elevation of plasma and urinary inorganic phosphorus levels in diabetic acidosis and a precipitous fall after insulin therapy have been demonstrated by others [13] and confirmed by our data. The probable mechanism of these changes was brought out by the findings of Guest and Rapoport [2b] and Kaplan, Franks and Friedgood.[2d] The former showed that the organic acid-soluble phosphorus compounds of the red blood cells fell markedly in diabetic acidosis and rose in response to insulin therapy. Using rats with diabetes induced by alloxan, the latter demonstrated that the development of coma was accompanied with a decrease in the organic phosphates of the liver (chiefly adenosine triphosphate and adenosine diphosphate) and an increase in the inorganic phosphate of the liver and plasma. Under insulin therapy the inorganic phosphate levels in the plasma and liver fell, while the organic phosphates of the liver increased. Thus, the elevation of the inorganic phosphate level in the plasma and urine during diabetic acidosis may be due to the breakdown (or failure of reconstitution) of organic phosphates because of the depressed oxidation resulting from lack of insulin. The fall in plasma and urinary inorganic phosphate levels during insulin therapy is probably due to the resumption of phosphorylation, with subsequent reconstitution of the organic phosphate compounds of the body.

During the development of diabetic acidosis, Atchley and others [2a] demonstrated an increase in urinary output of phosphorus sufficient to cause a significant depletion of this element. The presence of a considerable phosphorus deficit in diabetic acidosis was indicated by the data of Guest and Rapoport [2b] and by the observations reported in this communication. The patients who received sodium phosphate solution exhibited a great avidity for the phosphorus, which was apparently deposited rapidly in the tissues. The maximum rise in plasma inorganic phosphorus obtained with 2,638 mg. was 7.72 mg. per hundred cubic centimeters, as compared to the 10.10 to 17.86 mg. rise obtained in normal persons given the same quantity.[7] In the normal persons 55 to 68 per cent of the administered phosphorus was excreted in six to twelve hours. In our cases an average of only 28 per cent was recovered from the urine over a period of eighteen hours. Other avenues of excretion were not investigated but probably played only a minor role, since Hevesy,[10] using radioactive phosphorus as a tracer,

13. Kay, H. D., and Robison, R.: Effect of Insulin Administration on the Distribution of the Phosphorus Compounds of Blood and Muscle, Biochem. J. **18**: 1139, 1924. Perlzweig, W. A.; Latham, E. and Keefer, C. S.: Behavior of Inorganic Phosphate in the Blood and Urine of Normal and Diabetic Subjects During Carbohydrate Metabolism, Proc. Soc. Exper. Biol. & Med. **21**:33, 1923. Guest and Rapoport.[2b] Harrop and Benedict.[2c] Kaplan and others.[2d]

calculated that only one eighth of the phosphorus absorbed into the body was excreted by routes other than the urinary tract. Despite the administration of this supplemental phosphorus, subnormal urinary excretion persisted in all our cases throughout the period of study (six days in 1 case). From two to five days were required for the total urinary phosphorus output to equal the amount given intravenously, even though liberal amounts were included in the diet after the first day. Thus the significant phosphorus deficit associated with diabetic acidosis was only partially replenished by the amounts of phosphorus given to our patients.

In view of the importance of phosphorylated compounds in carbohydrate metabolism, a distinct improvement in carbohydrate utilization might be anticipated in the phosphate-treated patients. Indeed, Friedlander and Rosenthal [14] observed a fall in the blood sugar content in diabetic patients given infusions of sodium phosphate without insulin. We have confirmed this in a single unreported case. In this series of cases of diabetic acidosis the blood sugar was better controlled and carbohydrate appeared to be utilized more efficiently when phosphate was administered than when it was withheld. Since the total number is small and since individual cases in the phosphate and dextrose control groups differed considerably in initial severity and in dextrose and insulin dosage, the series must be extended before positive conclusions can be drawn in regard to the effect of exogenous phosphate on carbohydrate metabolism.

No acceleration in the rate of disappearance of acetonuria was demonstrable after the administration of sodium phosphate. The greater rise in carbon dioxide–combining power and the superior maintenance of plasma chloride levels are expected from the transfer of phosphate ion to the cells. This transfer leaves the sodium ion free to increase the alkaline reserve. Chloride and organic phosphate concentrations are in a reciprocal equilibrium, at least in the red blood cells. [15] Thus, when the organic phosphate level rises in the red cell, chloride shifts from cell to plasma. This presumably accounts, at least in part, for the maintenance of high serum chloride levels in the phosphate group despite the relatively low chloride intake. The greater hemodilution suggests that sodium phosphate may promote retention of water in the vascular bed. The mechanism remains obscure.

The most striking clinical effect was the rapid improvement in mental state which accompanied the administration of sodium phos-

14. Friedlander, I., and Rosenthal, W. G.: Ueber den Einfluss des Phosphorsaueresion auf dem Blut und Harnzucker des normalen und des diabetischen Organismus, Arch. f. exper. Path. u. Pharmakol. **112**:65, 1926.

15. Guest, G. M., and Rapoport, S.: Organic Acid Soluble Phosphorus Compounds of the Blood, Physiol. Rev. **21**:41, 1941; footnote 2*b*.

phate. This may be traceable to the fact that carbohydrate is the preferred if not the sole fuel for the brain.[16] When an increased supply of phosphate is made available to the central nervous system, an increased efficiency of phosphorylations and hence of carbohydrate utilization may result. The presumed metabolic improvement might be reflected in the clearing of consciousness.

A second important clinical effect of administration of phosphate is the apparent improvement in fatality rate. Although the number of cases is small, application of the "chi squared" test for statistical significance to the dextrose and phosphate groups with 30 to 60 per cent severity indexes gives a P (probability) value of 0.07, indicating that only a small chance exists that the lowering in fatality rate is independent of the administration of phosphate. Comparison of the phosphate group with the saline group in which the condition was of equal or lesser severity again shows an apparent improvement in fatality rate, but the difference is not statistically significant and could have been due to chance.

It is difficult to attribute the improved survival rate to any single one of the effects of phosphate administration described here. The replenishment of the lost phosphate probably brought about a more rapid restoration of the depleted phosphorylated compounds of the cells. As has been pointed out, these organic phosphates are important because of their role in intermediary metabolism and because they are the reservoirs of energy derived from metabolic processes.[1] Thus, any measure, such as administration of inorganic phosphorus, which may help the resynthesis of these energy-rich organic phosphates may aid in restoration of normal cellular function. The potential importance of restoration of organic phosphates is indicated by the work of LePage [17] on tissue analyses in rats subjected to traumatic shock. The animals that succumbed to shock had severe depletion of the energy-rich organic phosphates in the most vital organs, including the brain. The animals that survived the trauma showed the ability to readjust their organic phosphates rapidly after the shocking procedure.

Patients with diabetic coma may die in shock even after the abolition of ketosis, the establishment of normal blood sugar levels and the administration of apparently sufficient amounts of plasma, sodium chloride and water. The administration of sodium phosphate may fail to restore a falling blood pressure and may not prevent shock. This necessitates consideration of the possible etiologic role of other deficiencies, especially the potassium deficit which accompanies the devel-

16. Himwich, H. E., and Nahum, L. H.: The Respiratory Quotient of the Brain, Proc. Soc. Exper. Biol. & Med. **26**:496, 1929.

17. LePage, G. A.: Biological Energy Transformation During Shock, as Shown by Tissue Analyses, Am. J. Physiol. **146**:267, 1946.

opment of diabetic acidosis.[2a] Holler [18] recently reported a case in which the patient exhibited progressive muscular weakness and respiratory distress between the twelfth and twenty-first hour of treatment, at which time the serum potassium was found to be 2.5 milliequivalents. Prompt recovery followed the administration of potassium chloride. It is known that potassium, as well as phosphorus, follows dextrose into and out of the cells. It seems logical that potassium phosphate solutions might be of greater value than the sodium phosphate used in this study.

SUMMARY

The effect of the administration of buffered sodium phosphate solution, containing 1,319 to 2,638 mg. of phosphorus, has been studied in 16 cases of severe diabetic acidosis. Phosphorus, glucose, water and chloride balances are presented for 10 of these cases. The results are compared with those in control subjects who were treated with early administration of dextrose and in subjects not so treated, both groups receiving no sodium phosphate.

The plasma inorganic phosphorus level was elevated in all cases prior to treatment. A precipitous fall in the plasma level and in the urinary excretion occurred when insulin was given. The protracted subnormal phosphate excretion during convalescence reflected a profound depletion of phosphorus stores prior to treatment. A marked retention of injected phosphorus was demonstrated in all cases. Nevertheless, the dosage used was insufficient to correct completely the deficit, as shown by the subsequent drop in urinary inorganic phosphorus to subnormal levels.

The administration of sodium phosphate was accompanied with (*a*) a tendency toward improved utilization of carbohydrate, (*b*) a rise in plasma chloride and in carbon dioxide–combining power, (*c*) an apparent retention of fluid in the vascular system, (*d*) a rapid clearing of the mental state and (*e*) a statistically significant decrease in fatality rate.

The results of this study suggest that the therapeutic regimen in diabetic coma should include the parenteral administration of sodium phosphate four to eight hours after the first dose of insulin.

The results are discussed in the light of current opinion on the role of phosphate in carbohydrate metabolism.

18. Holler, J. W.: Potassium Deficiency Occurring During the Treatment of Diabetic Acidosis, J. A. M. A. **131**:1186 (Aug. 10) 1946.

CHRONIC RECURRENT PANCREATITIS

A Clinical Study of Twenty Cases

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CHRONIC pancreatitis is an entity characterized by recurrent episodes of pain in the upper part of the abdomen. The diagnosis is seldom considered clinically, presumably because of limited familiarity with the various manifestations of the disease. The purpose of this paper is to review the significant manifestations as observed in 20 patients and to direct attention to certain features which may be helpful in the diagnosis.

TABLE 1.—*Chronic Pancreatitis in Twenty Patients*

	Number
Sex	
Male	12
Female	8
Age, Yr.	
20 to 29	1
30 to 39	6
40 to 49	3
50 to 59	6
60 to 69	2
70 to 79	2

SEX AND AGE

The series comprises 12 men and 8 women. Reference to table 1 indicates that persons under 50 years of age were affected as often as those over 50. The predominance of males is in accord with other observations. Friedenwald [1] noted 14 males in a group of 25 patients and Vachon [2] 5 in a group of 6 patients, and Comfort and others [3]

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1. Friedenwald, J.: Acute and Chronic Pancreatitis, South. M. J. **30**:1067-1074, 1937.

2. Vachon, M. A.: Painful Forms of Chronic Pancreatitis, Lyon méd. **167**: 337-340, 1942.

encountered 25 in a series of 29. The age incidence, as given in the three reports, varied. While chronic pancreatitis was found in persons of all ages, its incidence appeared to be greater among those under 50.

DURATION OF SYMPTOMS

The duration of symptoms varied widely. In 8 patients the distress had been present for less than a year at the time of initial observation, while in 10 symptoms had been noted intermittently for three to five years. One man experienced repeated attacks of abdominal pain for ten years and another for thirty years. The intervals between acute attacks of pain ranged from two days to six months. Mild transitory abdominal discomfort and vague digestive disturbances, however, were present almost constantly in the majority of patients.

SYMPTOMS

Pain was the most frequent and outstanding complaint (table 2), occurring in 17 of the 20 patients (85 per cent). In 16 it was described

TABLE 2.—*Symptoms of Chronic Pancreatitis*

Symptoms	Percentage
Dyspeptic symptoms	100
Severe postprandial distress	85
Postprandial emesis	65
Loss of weight	60
Bouts of jaundice	40
Chills, sweats and fever	35

as severe, constant and knifelike; in 1 it was diffuse and indefinite. In 10 it was localized in the epigastrium, and in 6 others it was present in the right upper part of the abdomen. Pain in the back was the outstanding symptom in 1 instance. Radiation of pain was noted by 6 of the 17 patients. In 3 it was referred to the lumbar area from the level of the twelfth thoracic vertebra to the level of the second lumbar vertebra, and in 3 others it was transmitted to the right scapular and interscapular areas. The distribution of referred pain did not follow any distinct pattern. The left side of the hypochondrium, a frequent site of transmitted pain from the pancreas, was not mentioned as a point of transmission by any of this group. Pain in the back, commonly noted in pancreatic carcinoma, occurred in only 3 cases. In this series the acute episodes of pain averaged three to six hours in duration and occasionally persisted for from twenty-four to seventy-two hours. In only 2 patients was the acute attack of pain transitory, and in these it lasted less than thirty minutes. Frequently in persons with prolonged distress the recurrent pain steadily increased in severity and

3. Comfort, M. W.; Gambill, E. E., and Baggenstoss, A. H.: Chronic Relapsing Pancreatitis, Gastroenterology **6**:239-285 and 376-408, 1946.

eventually necessitated hospitalization. The diagnosis for 3 patients without abdominal pain was established by the roentgenologic demonstration of pancreatic calcifications. Steatorrhea was present in all 3 and diabetes in 2. It should be noted, however, that severe pain may occur in the presence of pancreatic calcification. Calculi were found in the pancreatic ducts at operation in 2 of the 17 patients with attacks of pain.

Dyspeptic symptoms such as bloating, eructation and vague abdominal distress were described by the entire group. In 16 postprandial discomfort was considerable, and in 13 the ingestion of moderate quantities of food precipitated acute attacks of pain. Partial relief from pain was obtained by emesis in 10. Small frequent feedings tended to prevent the postprandial distress; alkalis had little or no effect.

Alcohol has been regarded as one of the precipitating factors in pancreatitis by some investigators. Clark,[4] in a study of the postmortem findings in patients with chronic alcoholism, found 36 in whom pancreatitis was a contributing cause of death. In 19 it was acute, in 5 acute and chronic and in 9 chronic. In 3 fat necrosis was present. The ingestion of alcohol in large quantities was followed by severe and protracted bouts of pain in 2 of the present series. A history of the excessive ingestion of alcohol was not elicited for the remaining 18. In this series, therefore, alcohol seemed of little importance in the development of the disease.

Loss of weight occurred in 12 patients (60 per cent). In 8 without steatorrhea the losses varied up to 20 pounds (9 Kg.). In 4 with pancreatic insufficiency the loss of weight averaged more than 25 pounds (11 Kg.).

A history of recurrent jaundice with attacks of pain was obtained in 8 cases. It was moderate in 5 and severe in 3. Chills followed by fever and sweats preceded the icterus in 4. In 5 of the 8 patients obstruction of the common duct was observed at operation, but in no instance was there a stone present in the common duct. The operative findings are discussed in more detail later.

PHYSICAL EXAMINATION

The physical findings were varied, and no pathognomonic manifestations of pancreatitis could be discovered. Varying degrees of tenderness were noted during acute attacks of distress in the 17 patients with pain. In 5 of these with severe pain rigidity of the upper part of the abdomen was present. Three others with diffuse pancreatic calcification had no abdominal tenderness.

The liver was palpable in 3 patients at an average of 3 cm. below the right costal margin. Moderate jaundice was present in 2 of these.

4. Clark, E.: Pancreatitis in Acute and Chronic Alcoholism, Am. J. Digest. Dis. **9**:428-431, 1942.

While the incidence of a palpable mass in carcinoma of the pancreas is approximately 30 per cent, abdominal masses are infrequent in pancreatitis. In 1 patient a moderately firm irregular tumor, approximately 5 cm. in diameter, which descended on respiration was noted in the right side of the hypochondrium. Preoperatively this was interpreted as a pancreatic neoplasm. Exploration disclosed an inflammatory mass in the uncinate process of the pancreas, with involvement of the surrounding structures.

In another case a mass the size of a grapefruit was present in the epigastrium. The preoperative diagnosis of a pancreatic cyst was confirmed at operation.

Variations in temperature were not of sufficient regularity during the acute episodes to be of diagnostic significance. In 8 patients the temperature ranged from 100.5 to 103.2 F. during episodes of pain. There was no correlation between the degree of fever and the severity of the disease.

LABORATORY DATA

The serum amylase content was measured in 8 patients (table 3). Increase of the level to 1,500, 1,261 and 500 units respectively was noted in 3 cases. In 4 the levels were within normal limits (135, 125, 100 and 90 units), and in 1 a lowered value (40) was obtained.

Increase of the Serum Amylase Content.—The following 3 cases illustrate examples of increased serum amylase content.

CASE 11.—A 44 year old housewife had been subjected to a cholecystectomy one year previously. She was admitted to the hospital with severe abdominal pain. The temperature was 100.5 F.; the leukocyte count was 16,000. Four days after her admission pain was still present. The serum amylase content at that time was 1,500 units; the value on the fifth day was 45 units and on the eighth day 176 units. At operation (on the ninth day of hospitalization) the pancreas was found to be markedly thickened and fibrotic. There was no evidence of pancreatic necrosis or hemorrhage, and "fat necrosis" was absent.

CASE 3.—A 33 year old minister with recurrent severe epigastric pain had had an increased serum amylase level demonstrated elsewhere during a previous acute attack. The abdomen was tender but not rigid. The temperature was 99 F. and the leukocyte count 21,000. The serum amylase level on the day of his admission to the hospital was 1,261 units, and on the following day it was 1,240 units. The acute attack subsided within forty-eight hours.

CASE 1.—A 44 year old white woman had had recurrent attacks of distress in the upper abdominal area for three years. Physical examination revealed moderate abdominal tenderness and a mass the size of a grapefruit in the epigastrium. There was no fever or leukocytosis. The serum amylase level, determined eighteen days after her admission to the hospital, was 1,261 units. Operation several days later revealed a cyst together with induration of the pancreas; there was no gross evidence of acute pancreatitis.

The mechanism of the variations in amylase is not clear. The operative findings suggest, however, that they are determined by the changes

TABLE 3.—*Serum Amylase Content and Leukocyte Values with Clinical and Operative Data in Eight Cases*

Case	Diagnosis	Type of Pain	Temperature, F.	Condition of Abdomen	Diabetic State	Steatorrhea	Operative Findings *	Leukocyte Count †	Serum Amylase Content
11	Chronic pancreatitis	Prolonged and severe	100.5	Marked rigidity	No	No	Induration of the pancreas	16,000	1,500
3	Recurrent pancreatitis	Three severe attacks	99.0	Moderate tenderness	No	No	.....	21,000	1,261
1	Pancreatic cyst	Moderate	98.6	Epigastric mass (grapefruit sized)	No	No	Cyst of body of pancreas; diffuse induration	8,000	500
9	Obstruction of the common duct secondary to pancreatic cyst	Severe	98.6	Normal	No	No	Cyst of the uncinate process; diffuse induration of pancreas	13,000	135
6	Calcareous pancreatitis with steatorrhea	None	98.6	Normal	No	Yes	.....	.....	125
15	Calcareous pancreatitis with steatorrhea and a diabetic state	None	98.6	Normal	Yes (Mild)	Yes	.....	.....	100
16	Calcareous pancreatitis with steatorrhea and a diabetic state	None	98.6	Slight tenderness	Yes (Mild)	Yes	Diffuse fibrosis of the pancreas; ductal calculi	.....	90
17	Calcareous pancreatitis with steatorrhea and a diabetic state	Moderate	98.6	Slight tenderness	Yes (Mild)	Yes	Diffuse fibrosis of the pancreas; ductal calculi	13,000	40

* In cases 3, 6 and 15 no operation was performed.
† In cases 6, 15 and 16 the count was below 10,000.

in the degree of activity of the pancreatic disease rather than by progressive destruction of the pancreatic acinar tissue.

A normal or lowered amylase level is not incompatible with chronic progressive or recurrent pancreatitis. In 2 of 4 patients with repeated attacks of pain surgical exploration disclosed pronounced induration and fibrosis of the pancreas. The serum amylase values in these patients were not remarkable (table 3, cases 9, 6, 15 and 16). The value may be lowered in the presence of widespread acinar destruction. This was demonstrated in a 62 year old white man in whom marsupialization of a pancreatic cyst had been performed thirty years previously and who had undergone gastroenterostomy twenty years before his admission to the hospital. Steatorrhea had been present for the seven years prior to his admission. The serum amylase level was 40 units. Operation disclosed a diffuse fibrosis and thickening of the pancreas, with dilatation of the pancreatic ducts, which contained many calculi (table 3, case 17).

Oral Test for Glucose Tolerance.—The oral test for glucose tolerance was performed in 9 cases. A diabetic type of curve was observed in 8 and a flat curve in 1. The impression was gained from these cases that an elevated curve for glucose tolerance in association with recurrent episodes of pain in the upper part of the abdomen is suggestive of chronic pancreatitis.

The icterus index was increased in 7 of the 9 cases in which it was measured. The values ranged from 10 to 20 in 5 instances. Levels of 158 and 240 were noted for 2 patients, in both of whom the diagnosis of obstruction of the common duct was confirmed at operation. The findings in this series suggest that in addition to disease of the biliary tract chronic pancreatitis also should be considered in the differential diagnosis of obscure recurrent pain in the upper abdominal area associated with jaundice.

Urine.—Transitory glycosuria of varying degrees was present in 3 cases. In 1 of these, in which acute abdominal pain, leukocytosis (24,000) and increase of the serum amylase level (1,261 units) were present, the glycosuria subsided after forty-eight hours. In 5 patients with persistent glycosuria a diabetic state was demonstrated in addition to the pancreatitis.

Bilirubinuria in the presence of pancreatitis may indicate severe inflammation, especially of the uncinate process. It was present in 6 patients, in 4 of whom obstruction of the common duct secondary to chronic inflammation of the uncinate process of the pancreas was demonstrated at operation. In the remaining 2 the common duct was patent but the pancreas was diffusely indurated.

Leukocytosis.—The leukocyte count was increased in 12 patients, the values ranging from 11,600 to 23,410 and averaging 16,800. Acute active disease was present in 4 of these. It should be noted, however,

that the white blood cell count was normal in 8 patients despite the presence of active pancreatitis. In case 1, in which there were an increased amylase level, recurrent pain and a pancreatic cyst, the count was less than 10,000. In case 2 the leukocyte count was normal in the presence of attacks of pain and severe jaundice. Operation revealed an indurated inflammatory mass involving the head of the pancreas. The patient in case 13, with a history of chills, fever and jaundice, exhibited moderate icterus and loss of weight on admission to the hospital. There was no fever or leukocytosis. At operation the pancreas was indurated but the common bile duct was patent. The leukocyte count was normal in the patient in case 19, who had extensive pancreatic inflammation, an external biliary fistula and a temperature on admission to the hospital of 99.4 F.

ROENTGENOLOGIC MANIFESTATIONS

Cholecystogram.—There was no constant relationship between the roentgenologic visualization of the gallbladder and the presence of pancreatitis (table 4). Nonvisualization after the oral administration of dye occurred in 5 cases (table 4, cases 6, 7, 14, 17 and 18). A roentgenogram in 1 of these (case 7) demonstrated densities in the right upper area of the abdomen suggestive of cholelithiasis. At operation the gallbladder was distended and adherent to the first portion of the duodenum, but it did not contain calculi. In another (case 14) the gallbladder was normal at operation, but the ampulla of Vater was obstructed by a pancreatic calculus. In a third case (case 17) surgical exploration disclosed a moderately thickened and and inflamed gallbladder which contained calculi, while in a fourth (case 18) postmortem examination revealed a thin-walled, apparently normal gallbladder but moderately dilated cystic and common ducts. Thus, in 3 of the 4 patients operated on in whom there was nonvisualization of the gallbladder no primary cholecystic disease was found. Cholelithiasis was noted at operation in 2 of 5 other patients in whom there was normal visualization of the gallbladder (cases 5 and 10). In 1 of these (case 10) fat necrosis was present in the upper part of the abdomen in addition to the induration of the pancreas.

Gastroduodenal Examination.—Abnormalities were found in 3 of 13 patients who had gastroduodenal examinations (table 4). The first (case 1) exhibited displacement of the lesser curvature by a mass posterior to the stomach (pancreatic cyst). In the second (case 7) there was dilatation of the stomach and of the first portion of the duodenum, which was due to narrowing of the second portion of the duodenum, by an inflammatory mass involving the uncinate process of the pancreas. In the third patient (case 8) the roentgen examination revealed dilatation of the second portion of the duodenum, demonstrated at operation to be due to an inflammatory process which narrowed the third portion.

Small Intestine.—In case 13 roentgenologic studies of the small bowel revealed distention of the loops in the left side of the abdomen. At operation diffuse firm nodular induration of the pancreas was noted, but no mention was made of the intestine. The relationship of a prob-

TABLE 4.—*Roentgenologic Manifestations*

Case	Esophagus	Stomach	Duodenum	Small Bowel	Gallbladder	Pancreatic Calcification
1	Normal	Posterior mass displacing the lesser curvature	Normal	Not examined	Visualized; no calculi	None
2	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined
3	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined
4	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined
5	Not examined	Not examined	Not examined	Not examined	Normal visualization after cholecystostomy	None
6	Normal	Normal	Normal	Not examined	Not visualized	Diffuse calcification
7	Normal	Dilated	Second portion narrowed	Not examined	Not visualized; opaque stones present	Diffuse calcification
8	Normal	Normal	Dilatation of second portion	Not examined	Not examined	None
9	Normal	Normal	Normal	Normal	Not examined	Calcified flecks to the right of the second lumbar vertebra
10	Normal	Normal	Normal	Normal	Visualized; calculi present	None
11	Normal	Normal	Normal	Not examined	Not examined	None
12	Normal	Normal	Normal	Not examined	Not examined	None
13	Normal	Normal	Normal	Dilated loop of jejunum	Not examined	None
14	Normal	Normal	Normal	Not examined	Not visualized	Small calcification to the right of the second lumbar vertebra
15	Normal	Normal	Normal	Not examined	Visualized; no calculi	Diffuse moderate calcification
16	Normal	Normal	Diverticulum of second portion	Normal	Visualized; no calculi	Calcified flecks to the left of the second lumbar vertebra
17	Normal	Functioning gastroenterostomy	Normal	Not examined	Not visualized	Branching calculi to the right of the second lumbar vertebra
18	Not examined	Not examined	Not examined	Not examined	Not visualized	Not examined
19	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined
20	Not examined	Not examined	Not examined	Not examined	Not examined	Not examined

able stenotic process of the small intestine to panreatic inflammation is unknown. (A roentgenogram of the abdomen in 1 case demonstrated distended loops of small bowel suggestive of an obstruction.)

Pancreatic Calcification.—Calcifications were found localized in various parts of the pancreas in 4 cases, and they diffusely involved

the organ in 3 others (table 4). There was no uniform pattern in the arrangement of the calcification, and the differentiation between calculi in the ducts and parenchymal calcifications could not be made clinically. Normal visualization of the gallbladder was observed in patients with calcification in the pancreatic ducts as well as in the parenchyma. Two of these (cases 6 and 15), with diffuse calcific changes, manifested steatorrhea and diabetes. However in a third (case 7), in whom there were similar calcifications and a stenosing duodenal lesion, pancreatic function was not changed. In a fourth patient (case 9), with small calcified flecks to the right of the second lumbar vertebra, a cyst of the uncinate process was found at operation, the calcified particles being located in the wall of the cyst. Roentgen study of the fifth patient (case 14) revealed a small indefinite shadow to the right of the first lumbar vertebra. Postmortem examination disclosed a small calculus in Wirsung's duct compressing the common duct. In 2 patients (cases 16 and 17) multiple pancreatic calculi were demonstrated at laparotomy. Pain was a promiment clinical feature in both of these. Diffuse fibrosis, dilatation of the ducts and pancreatic insufficiency were present in each instance.

RELATION OF CHRONIC PANCREATITIS TO METABOLIC DISTURBANCES

In 10 patients of the group (50 per cent) mild to significant disturbances in carbohydrate metabolism were found; in 3 (cases 1, 10 and 13) the curves for glucose tolerance were elevated. In 1 (case 1) the curve returned to normal after marsupialization of a pancreatic cyst. Mild diabetes was present in 4 patients (cases 6, 17, 18 and 19). More advanced diabetes was present in 3 (cases 15, 16 and 20). Pancreatic calcifications were present in 4 of the 7 patients with diabetes.

Steatorrhea was present in 5 cases (25 per cent). Pancreatic calcifications were demonstrated in 4 of these, and a diabetic state was present in the entire group. The ages of the patients with steatorrhea ranged from 54 to 75 years, averaging 60 years at the time of their admission to the clinics, in contrast to an average age of 42 years for patients without calcification and steatorrhea.

INCIDENCE AND TYPE OF PREVIOUS SURGICAL PROCEDURES

Various surgical procedures (table 5) had been performed previously on 10 patients (50 per cent) of the group in an unsuccessful effort to alleviate the symptoms. Bilateral salpingectomy had been performed on 1 (case 1) and exploratory laparotomy on another for a suspected perforated ulcer. In a third case (case 17) marsupialization of a pancreatic cyst had been done thirty years previously and a gastroenterostomy twenty years before the present admission of the patient to the hospital. In a fourth (case 7) there was a history of an exploratory operation having been carried out ten years earlier.

Operation on the biliary tract had been performed previously in 6 cases. Cholecystectomy had been done in 4. In 3 of these the procedure had been carried out at other institutions and it was not known whether gallstones were present or not. In 2 cases there were no calculi in the gallbladder. Cholecystostomy had been done in 1 case (case 19) and cholecystogastrostomy in another; large solitary gallstones were present in both instances.

RELATION OF PREVIOUS OPERATION ON THE BILIARY TRACT TO THE PRESENT OPERATIVE FINDINGS

The interval between the first and the second operation in the 6 patients varied from three months to five years. In 3 the interval was less than one year (cases 14, 19 and 20) and in 3 others less than two years (cases 8, 11 and 13), and in 1 (case 12) it was five years.

The status of the biliary tract, as determined at the second operation, merits further comment (table 6). In case 11 (cholecystectomy had been performed one year previously) the common duct was normal in

TABLE 5.—*Previous Surgical Procedures*

Procedure	Number of Cases
Cholecystectomy	4
Cholecystostomy	1
Cholecystogastrostomy	1
Exploration	2
Salpingectomy	1
Marsupialization of pancreatic cyst	1

size and patent throughout and the pancreas was diffusely indurated. In case 12 (cholecystectomy five years before the patient's admission to the hospital) laparotomy revealed a completely normal common duct; the head of the pancreas was unusually firm and nodular.

The common duct was enlarged in 2 cases. The patient in case 8 had undergone cholecystectomy twenty months before the present operation. The common duct was dilated and measured 2.5 cm. in diameter; however careful probing revealed complete patency of the duct passage into the duodenum. The pancreas again was firm and diffusely indurated. In case 13 cholecystectomy had been performed eighteen months before the patient's admission to the hospital. As in the preceding case, the common duct averaged 2.5 cm. in diameter and was patent throughout and the head of the pancreas was enlarged and indurated. Jaundice had not occurred in these 2 cases.

Operation in case 19 (cholecystostomy four months earlier) disclosed a normal and patent common duct, but the pancreas was firm and indurated as described at the first operation. In case 20 (cholecystogastrostomy five months earlier) adhesions and fibroplasia so involved the portal structures that proper identification was rendered difficult and incomplete.

TABLE 6.—*Diagnosis and Clinical Course in Twenty Patients with Recurrent or Chronic Pancreatitis*

Case	Preoperative Diagnosis	Postoperative Diagnosis	Surgical Procedure	Pathologic Changes Present	Postoperative Course
1	Pancreatic cyst	Pancreatic cyst	Marsupialization of cyst	Grapefruit-sized pseudocyst of the midpancreas	Symptom free—followed for 6 mo.
2	Carcinoma of the head of the pancreas	Interstitial pancreatitis	First stage of pancreatic duodenectomy; gastroenterostomy and cholecystojejunostomy	Induration of head of pancreas (inflammatory)	Symptoms relieved
3*	Recurrent pancreatitis	.....	.....	.....	Recurrent attacks
4	Perforated peptic ulcer	Pancreatitis, interstitial with edema	Exploration	Edema, induration and slight hemorrhagic areas	Attacks gradually decreased but recurred for 2 yr.
5	Cholecystitis and cholelithiasis	Cholecystitis, cholelithiasis, pancreatitis and fat necrosis	Cholecystostomy	Bile-stained turbid fluid around the gallbladder; diffuse fat necrosis; edema of pancreas	No recurrence—followed for 6 yr.
6*	Pancreatic calcification	.....	.....	.....	No change in 3 yr.
7	Duodenal obstruction, cause undetermined	Pancreatitis with induration of uncinate process	Cholecystectomy and posterior gastroenterostomy	Dilatation of the stomach; patulous pylorus, dilated duodenum and dilated common duct; interstitial pancreatitis	Improved—followed for 2 mo.
8	Stone in the common duct	Diffuse interstitial pancreatitis	Choledochostomy	Common duct dilated but patent throughout; marked diffuse induration of pancreas	Marked improvement, but occasional attack of pain recurred for 6 mo.
9	Stone in the common duct? Carcinoma of the head of the pancreas?	Diffuse interstitial pancreatitis—pseudocyst, head of pancreas	Cyst marsupialized; cholecystojejunostomy	Fist-sized pseudocyst of head of pancreas, dilatation of common duct and diffuse induration of pancreas	Relief of jaundice; no recurrence
10	Cholelithiasis and cholecystitis	Cholelithiasis, diffuse indurative interstitial pancreatitis	Cholecystostomy	Cholelithiasis; fat necrosis; pancreas small and diffusely indurated	No recurrence for 3½ yr.

11	Injury of the common duct, or stone; pancreatitis	Diffuse interstitial pancreatitis	Choledochostomy	Common duct normal; diffuse induration of the pancreas	No symptoms for 6 mo.
12	Stone in the common duct	Interstitial nodular pancreatitis uncinate process chiefly involved	Choledochostomy	Common duct patent; induration and enlargement of uncinate process	Slight improvement; recurrent attacks
13	Stone in the common duct	Indurative interstitial pancreatitis	Choledochostomy	Common duct dilated and patent throughout; head of pancreas indurated and enlarged	No improvement
14	Obstruction of the common duct	Obstruction of the common duct; indurative pancreatitis	Choledochoduodenostomy	Stone in pancreatic duct below the opening of the common duct, with compression of the duct	Peritonitis; separation of anastomosis; death 10 days postoperatively
15*	Diabetes, steatorrhea and pancreatic calcification	.....	.....	.....	Improved with large doses of pancreatin
16	Diabetes, steatorrhea and pancreatic calcification	Interstitial pancreatitis; pancreatic calculi	Removal of pancreatic calculi	Induration of head of pancreas; 10 to 15 calculi in the pancreatic duct; duct system dilated	Diabetes unchanged; steatorrhea improved 1 year later
17	Obstruction of the pancreatic duct	Cholecystitis and cholelithiasis; pancreatic calculi	Cholecystectomy; removal of pancreatic calculi	Thickened and inflamed gallbladder; dilated pancreatic duct containing many calculi; fibrosis of pancreas	Steatorrhea moderately improved but continued attacks of pain disappeared
18	Cholecystitis with cholelithiasis; coronary thrombosis	Massive suppuration of pancreas (postmortem)	Autopsy	Autopsy—suppurative pancreatitis, dilatation of common duct and ampulla of Vater, biliary cirrhosis and thrombosis of mesentery and portal veins	Repeated attacks of epigastric pain for 3 mo. prior to death
19	Pancreatitis, chronic cholecystitis and obstruction of the cystic duct	Chronic cholecystitis; chronic pancreatitis	Cholecystectomy and enteroenterostomy	Induration of pancreas; some thickening of gallbladder	Died 6 days later—Friedländer septicemia, acute and chronic pancreatitis and dilatation of pancreatic duct (autopsy)
20	Carcinoma of pancreas, with metastases	Chronic pancreatitis; hyperplastic peritonitis	Exploration	Diffuse inflammatory mass	Died 18 days postoperatively

* In cases 3, 6 and 15 no operation was performed.

The unusual dilatation of the common duct, without obstruction, observed in cases 8 and 13 is of interest and may represent an adaptation by the choledochus to the function of the gallbladder. It is to be noted, however, that in 2 other cases, referred to previously, the common ducts were normal after cholecystectomy. The interval between cholecystectomy and the dilatation of the duct seems to be of little importance, for the dilated bile ducts were found twenty and eighteen months after operation in cases 8 and 13 while in cases 11 and 12 normal ducts were found twelve and sixty months after removal of the gallbladder. No explanation can be offered for these variable findings. The mechanism of dilatation of the common duct after cholecystectomy has been the subject of considerable investigation. Rothman,[5] in a review of the mechanism of pain after cholecystectomy, found evidence of a disturbed choledochal sphincter in some instances. After cholecystectomy the common duct has been shown to dilate as the sphincter muscle, because of hypertonicity and hypertrophy, intermittently retards the flow of bile. The role of the pancreatitis in the production of dilatation is obscure. Conceivably in some cases both may result from the same mechanism, i. e., a disturbance in the sphincter of Oddi with a "common channel." However the absence of dilatation of the common duct in 2 patients with pancreatitis does not support this hypothesis.

SURGICAL PROCEDURES AND RESULTS

Surgical exploration was performed in 16 of the 20 patients. The operative procedures are listed in table 7. Drainage of the common duct or of the gallbladder was performed in 6; anastomosis of the common duct or gallbladder to the intestinal tract was accomplished in 3.

Obstruction of the common duct with jaundice following chronic induration or fibrosing pancreatitis is an infrequent finding. It was present in 2 cases of the series. Cholecystojejunostomy relieved the obstruction in both cases. Peterson and Cole[6] report obstruction in 3 cases. Walters, in a study of 80 patients with stricture of the common duct, found that in none was the condition due to pancreatitis while in 1 it was secondary to a calcified pancreatic cyst.[6]

COMMENT

The present analysis indicates certain clinical aspects which may be of importance in the diagnosis of recurrent pancreatitis.

Bouts of severe pain in the upper abdominal area are noted in almost all patients. These tend to recur over a prolonged period, which

5. Rothman, M. M., in Bockus, H. L.: Gastroenterology, Philadelphia, W. B. Saunders Company, 1946, vol. 3, pp. 514-530.

6. Peterson, L. W., and Cole, W. H.: Chronic Sclerosing Pancreatitis Causing Stenosis of the Common Bile Duct, Arch. Surg. **51**:15-21 (July) 1945.

averaged four years in 60 per cent of the present series. The duration of the disease prior to diagnosis has been reported by others to vary from five to seven years. The pain is usually sharp and unremittant, and sometimes it is boring. Characteristically, it is prolonged, lasting three hours or more, and little or no relief is obtained from opiates. Radiation of pain is frequently present but without a definite pattern of distribution. The initial diagnoses are shown in table 6, as are the operative findings and the postoperative course.

In approximately 50 per cent of cases a previous laparotomy has been performed which failed to relieve the symptoms or establish the diagnosis. The importance of considering the possibility of pancreatitis in the treatment of patients with pain in the upper part of the abdomen following operation on the biliary tract is evident. The value of careful exploration of the pancreatic region in patients with a syndrome suggestive of biliary colic in whom laparotomy fails to disclose gallstones is to be emphasized.

TABLE 7.—*Operative Results in Chronic Pancreatitis*

Operation	Cases	Relieved	Improved	No Change	Deaths
Marsupialization of pancreatic cyst	1	1	..	..	..
Marsupialization and cholecystojejunostomy	1	1	..	..	..
Gastroenterostomy and cholecystojejunostomy	1	1	..	..	..
Exploration	2	..	..	1	1
Cholecystostomy	2	2	..	..	..
Cholecystectomy and posterior gastroenterostomy	1	1	..	..	..
Cholecystectomy and enteroenterostomy	1	..	..	..	1
Choledochostomy	4	1	1	2	..
Choledochoduodenostomy	1	..	..	..	1
Removal of pancreatic calculi	1	..	1	..	..
Removal of pancreatic calculi and cholecystectomy	1	..	1	..	..
	16	7	3	3	3

The difficulty of differentiating between benign and neoplastic pancreatic lesions may be great, since 35 per cent of the present series had abdominal pain, loss of weight and jaundice, symptoms frequently noted in carcinoma. Musser [7] reported pain to be the chief complaint in 100 cases of carcinoma of the pancreas without jaundice. Colic-like pain was present, with involvement of the pancreatic ducts, and pain in the back with involvement of the body and tail of the pancreas. Pain in the left upper abdominal area was not infrequent in the presence of pancreatitis.

Jaundice of varying degree may occur in chronic pancreatitis in the absence of obstruction of the common duct, an observation made in 4 patients. In 3 others the common duct was obstructed by an indurated fibrotic inflammatory process of the head of the pancreas. Walters and Dehne [7] found that 15 per cent of 113 patients with jaundice due to obstruction of the common duct secondary to lesions of the pancreas

7. Musser, J. H., cited by Walters, W., and Dehne, E. A.: Jaundice Caused by Pancreatic Lesions, Surg., Gynec. & Obst. **54**:832-835, 1932.

survived for five years or more, which indicated that the lesion was benign. In 99 of the 113 the jaundice was painless.

Certain laboratory procedures are of value in the differential diagnosis. A persistent increase in the blood sugar level, such as is noted in diabetes, is frequently observed after a glucose tolerance test.

Our limited experience confirms the generally accepted importance of high amylase levels in the diagnosis of pancreatic disease, especially during the acute episodes. Two patients with increased amylase levels had decided pancreatic induration at operation. It is important to realize, however, that the presence of a normal or lowered amylase content is not incompatible with active pancreatic disease, as was demonstrated in 5 cases in which the diagnosis was confirmed at operation. Elman [8] has found experimentally that the blood amylase content may double within fifteen minutes, quadruple in an hour and reach a level which is twenty times the normal one within twenty-four hours after complete obstruction of the pancreatic duct. Indeed, even simple palpation of the pancreas during operation may cause a transient but definite increase in the amylase level. In acute transient pancreatitis increased amylase values have been found at the height of the attack, with a return to normal as the process subsided. A rise in the amylase level followed by abnormally low levels has been observed in acute necrosis of the gland. Increased amylase values may indicate obstruction of the pancreatic duct, while lowered levels may suggest destruction of acinar tissue. Walters and Cleveland [9] report the serum amylase and lipase contents to be of diagnostic value during the first seven to ten days after an attack of pancreatitis; the amylase content returns to normal sooner than the lipase content. Comfort and others [3] found the serum amylase to be increased during acute attacks in 8 patients and between attacks in 3 among a group of 22. Variations between 60 and 150 units (Somoygi) have been considered normal for the serum amylase level at the University clinics. Levels below 50 and above 200 are suggestive of pancreatic disease but are not conclusive.

Roentgenograms of the upper part of the gastrointestinal tract may demonstrate constriction of the duodenum by fibrosing pancreatic lesions and displacement of the lesser curvature by a pancreatic cyst. Metheny and others [10] have described changes consisting of pressure on the greater curvature, duodenal ileus and enlargement of the duodenal loop during episodes of acute pancreatitis. They suggest that they are

8. Elman, R.: The Diagnosis and Treatment of Acute Non-Hemorrhagic Pancreatitis, Am. J. Digest. Dis. **4**:732-736, 1938.

9. Walters, W., and Cleveland, W. H.: Surgical Lesions of the Pancreas: A Review, Arch. Surg. **42**:819-838 (May) 1941.

10. Metheny, D.; Roberts, E. W., and Stranahan, A.: Acute Pancreatitis with Special Reference to X-Ray Diagnosis, Surg., Gynec. & Obst. **79**:504-508, 1944.

related to edema of the pancreas, which may enlarge to three times its normal size.

Pancreatic calculi are present in approximately one third of the patients with chronic pancreatitis and are readily demonstrated by a simple roentgenogram of the upper part of the abdomen. Ductal calcifications often are larger and more definite than diffuse parenchymal calcifications, attaining a diameter of 1 cm. or more. The differentiation between ductal and parenchymal calcifications is, however, usually not possible clinically. Pasternack [11] has noted that pancreatic calcification may form in less than one to two years.

An increased incidence of steatorrhea and of the diabetic state in pancreatitis and pancreatic calculi is noted in 25 to 50 per cent of the cases. Haggard and Kirtley [12] found glycosuria in 9.2 per cent of patients with pancreatic calculi. Pasternack reported diabetes in 50 per cent of patients with calcifications, while Snell and Comfort [13] noted diabetes in 8 and fatty diarrhea in 8 of a total of 18 patients. Pancreatic calcification was noted at autopsy in 5 of 16,000 patients by King and Waghelstein.[14] Pascucci,[15] in a review of 117,031 autopsies, recorded 52 cases (0.044 per cent) of pancreatic calculi. Pancreatic cysts were present in 0.061 per cent of 29,487 patients at autopsy. The cysts did not appear to be the sequela of calculi.

The value of cholecystectomy in the presence of pancreatitis requires further consideration. Removal of the gallbladder usually does not relieve the symptoms. Behrend,[16] in discussing the relationship of chronic pancreatitis to disease of the common duct, stated that cholecystoduodenostomy is the procedure of choice for patients with recurrent colic who at operation are found to have a noncalculous gallbladder. Vuori [17] found acute pancreatitis in 4 patients who had been subjected to cholecystectomy one and a half to four years earlier. In a study of 46

11. Pasternack, J. G.: Report of Three Cases of Calcareous Pancreatitis with Autopsies, Ann. Int. Med. **19**:757-767, 1943.

12. Haggard, W. D., and Kirtley, J. A., Jr.: Pancreatic Calculi: A Review of Sixty-Five Operations and One Hundred and Thirty-Nine Non-Operative Cases, Ann. Surg. **109**:809-826, 1939.

13. Snell, A. M., and Comfort, M. W.: The Incidence and Diagnosis of Pancreatic Lithiasis: Review of Eighteen Cases, Proc. Staff Meet., Mayo Clin. **17**: 209-211, 1942.

14. King, A. B., and Waghelstein, J. M.: Calcification of the Pancreas, Arch. Int. Med. **69**:165-176 (Feb.) 1942.

15. Pascucci, L. M.: Pancreatic Cysts and Lithiasis, Am. J. Roentgenol. **52**: 80-87, 1944.

16. Behrend, M.: Diseases of the Common Bile Duct and Their Relation to the Gastrointestinal Tract with Special Reference to the Role of Chronic Pancreatitis, J. A. M. A. **116**:204-208 (Jan. 18) 1941.

17. Vuori, E. O.: Four Cases of Acute Pancreatitis in Four Cholecystectomized Patients: Recurrence in Forty-Six Cases of Acute Pancreatitis, Acta chir. Scandinav. **88**:220-226, 1943.

cases of acute pancreatitis, he made a comparative analysis regarding recurrence or chronicity in patients who had undergone cholecystectomy and in those on whom this operation had not been performed. He concluded that cholecystectomy is of little prophylactic importance either in the primary or in the recurrent condition.

Surgical intervention gives good results in patients with obstruction of the common duct and in those with constriction of the duodenum. Removal of ductal calculi frequently relieves pain, while steatorrhea may be favorably affected. An established diabetic state tends to remain unaltered.

SUMMARY

In a group of 20 patients with chronic pancreatitis there were 12 men and 8 women. Fifty per cent were below 50 years of age.

Symptoms had been present for less than one year in 40 per cent; in the remaining 60 per cent the average duration was four years.

Recurrent bouts of severe pain in the upper abdominal area constituted the chief complaint in 85 per cent of the group.

The physical findings were indefinite and noncontributory. Jaundice of varying degree was present in 25 per cent of the patients.

The serum amylase content, determined in 8 patients, was increased in 3, normal in 4 and decreased in 1.

The oral test for glucose tolerance, carried out in 9 instances, yielded a diabetic type of curve in 8 and a flat curve in 1.

Pancreatic calcifications were demonstrated roentgenologically in 35 per cent of the cases.

Disturbances of carbohydrate metabolism were present in 10 of the 20 patients, a mild diabetic state being found in 4 and a more severe type in 3. In the remaining 3 glycosuria was transitory.

Steatorrhea was present in 25 per cent of the group.

Half of the patients had had previous surgical treatment, without relief of the abdominal pain.

CONCLUSIONS

1. Recurrent pancreatitis tends to pursue a prolonged and chronic course.

2. The condition is characterized by repeated bouts of severe pain in the upper part of the abdomen.

3. A diabetic type of curve following the oral test for glucose tolerance in the presence of such bouts suggests the presence of pancreatitis.

4. Pancreatic calcifications are not infrequently found roentgenologically.

5. Disturbances of carbohydrate metabolism are frequent.

6. Steatorrhea is not uncommon.

7. The possibility of pancreatitis must be especially considered in cases in which the patient continues to have attacks of pain simulating that of biliary colic after cholecystectomy has been performed.

ACUTE MEGAKARYOCYTIC LEUKEMIA

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LOS ANGELES

THERE have been many observations in medical literature in which megakaryocytes have been described as a prominent feature in pathologic conditions of the blood. The number of these cells is frequently increased in thrombocytothemia and polycythemia vera. Their presence in the bone marrow, liver, spleen and other viscera has been mentioned in numerous articles on myelogenous leukemia and various other diseases. Although the classification of leukemias by most American authors, including Bethell,[1] Downey,[2] Forkner,[3] Kolmer,[4] Kracke,[5] Osgood,[6] Levin[7] and Wintrobe,[8] recognizes the possibility of megakaryocytic leukemia, the specific criteria necessary for such a diagnosis are not stated in detail.

Von Boros and Korényi[9] reported a condition in 1931 which they designated as "acute megakaryoblastic leukemia," but the authenticity of the case has been questioned by American hematologists owing to lack of sufficient data.

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1. Bethell, F. H.: Leukemia: The Relative Incidence of Its Various Forms, and Their Response to Radiation Therapy, Ann. Int. Med. **18**:757 (May) 1943.

2. Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 1273.

3. Forkner, C. E.: Leukemia and Allied Diseases, New York, The Macmillan Company, 1938.

4. Kolmer, J. A.: Clinical Diagnosis and Laboratory Examination, New York, D. Appleton-Century Company, Inc., 1944, p. 689.

5. Kracke, R. R., and Gower, H. E.: Diseases of Blood and Atlas of Hematology, Philadelphia, J. B. Lippincott Company, 1937, p. 304.

6. Osgood, E. E., and Ashworth, C. M.: Atlas of Hematology, San Francisco, J. W. Stacy, Inc., 1937, p. 145.

7. Levin, V., in discussion on papers of Kracke and Graver, Rosenthal and Harris and Haden, J. A. M. A. **104**:709 (March 2) 1935.

8. Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, Lea & Febiger, 1946, p. 703.

9. von Boros, J., and Korényi, A.: Ueber einen Fall von akuter Megakaryoblastenleukämie, zugleich einige Bemärkungen zum Problem der akuten Leukämie, Ztschr. f. klin. Med. **118**:697, 1931.

Lindeboom [10] in 1938 noted that giant cells of megakaryocytic type were prominent features in a group of cases of a disorder designated as "aleukemic megakaryocytic leukemia" and suggested that this should be considered as a disease entity.

Kopäc [11] reviewed the German literature in 1943 and presented a case in which giant cells were present in leukemia. He concurred with the authors Körner,[12] Matthaeus [13] and Wienbeck [14] that the giant cells were basically megakaryocytes, even though other German authors, including Barth,[15] Matousek,[16] Krondel,[17] Esbach [18] and Dubinskaja,[19] considered them to be identical with reticuloendothelial cells.

The case that Barth reported has since been disregarded because the disease therein was spoken of as "endotheliosis with myelogenous leukemia."

Previous cases cited as instances of megakaryocytic leukemia and the case presented here are not to be confused in the nosologic system with cases classified under the following titles: myeloid megakaryocytic hepatosplenomegaly,[20] aleukemic myelosis with osteosclerosis,[21] megakaryocytic myelosis with osteosclerosis,[22] chronic nonleukemic myelosis [23] and leucoerythroblastic anemia with myelosclerosis.[24]

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10. Lindeboom, G. A.: Ueber die sogenannte aleukämische megakaryocytäre Myelose, Acta med. Scandinav. **95**:388, 1938.

11. Kopäc, Ueber die Bedeutung der Megakaryocyten-Leukämien, Virchows Arch. f. path. Anat. **310**:3 (July) 1943.

12. Körner, K.: Auffallende Riesenzellenbefunde bei akuten Myeloblastenleukämie, Virchows Arch. f. path. Anat. **259**:617, 1926.

13. Matthaeus, H.: Zur Kenntnis der Riesenzell-Leukämien, Beitr. z. path. Anat. u. z. allg. Path. **101**:189, 1938.

14. Wienbeck, J.: Die menschlich Leukämie, Jena, Gustav, Fischer, 1942; cited by Kopäc.[11]

15. Barth, H.: Virchows Arch. f. path. Anat. **356**:693, 1925; cited by Kopäc.[11]

16. Matousek, V.: Beitr. z. path. Anat. u. z. allg. Path. **106**:332, 1942; cited by Kopäc.[11]

17. Krondel, A.: Beitr. z. path. Anat. u. z. allg. Path. **106**: 332, 1942; cited by Kopäc.[11]

18. Esbach, H.: Virchows Arch. f. path. Anat. **303**:706, 1939; cited by Kopäc.[11]

19. Dubinskaja, B.: Ueber die Riesenzellenformen der Myelose, Virchows Arch. f. path. Anat. **270**:192, 1928.

20. Downey, H., and Norland, M.: Hematologic and Histologic Study of a Case of Myeloid Megakaryocytic Hepato-splenomegaly, Folia haemat. **62**:1, 1939. Chini, V.: La mielosi aleucemica megacariocitaria, Policlinico (sez. med.) **43**:257 (June) 1936.

21. Stephens, D. J., and Bredeck, J. F.: Aleukemic Myelosis with Osteosclerosis, Ann. Int. Med. **6**:1087 (Feb.) 1933. Lindeboom.[10]

22. Hewer, T. F.: Megakaryocytic Myelosis with Osteosclerosis, J. Path. & Bact **45**:383 (Sept.) 1937.

(Footnotes continued on next page)

It is not in the realm of this paper to discuss either the origin and maturation of the megakaryocytes or the cause of leukemia. We shall, however, present a case because it demonstrates the following unusual and interesting features: (1) absence of splenomegaly and lymphadenopathy; (2) slight hepatomegaly; (3) absence of osteosclerosis and osteofibrosis; (4) no history or evidence of a chronic granulomatous disease or of exposure to drugs; (5) marked anemia, with presence of numerous immature erythrocytes; (6) leukopenia, with immature myeloid cells; (7) thrombopenia, with atypical platelets; (8) erythromyelomegakaryocytic hyperplasia of the bone marrow, and (9) evidence at necropsy of extramedullary megakaryocytic infiltrations into other viscera. After careful analysis of the case to be presented, it is apparent that the condition does not fit into the aforementioned categories of disease and therefore necessitates a revision of the classification of leukemia to include megakaryocytic leukemia, not as a possibility, but as a clinical entity.

As far as we can determine, this is the first such case to be reported in the American literature.

REPORT OF A CASE

D. M., a 66 year old white married man, an actor, was first seen in the clinic early in 1936. He was born in Scotland. His father died at 70 years of age of unknown cause. His mother died at 68 years of cancer of the stomach. His childhood illnesses were of the usual variety and irrelevant to the present illness.

His first visit to the clinic was for epistaxsis, which was a local problem and responded to cauterization. At this time he stated that his general health had always been excellent. He was a small man and prided himself on his physical prowess, having been a professional tumbler at one time.

In February 1941 he was admitted to the Hollywood Presbyterian Hospital for treatment of lobar pneumonia. He responded to sulfathiazole therapy and was discharged at the end of one week. At this time laboratory findings were within normal limits (table 1).

In January 1943 the patient was again admitted to the hospital for approximately one week, with a clinical diagnosis of bronchopneumonia, which responded readily to therapy.

In May 1946 he was seen in the clinic for pain on movement of his neck. He attributed this pain to the possibility of a slight injury and stated that he had been "pushed around a bit while attempting to pass a picket line." The physical condition

23. Favre, M.; Croizat, P., and Guichard, A.: La myélose aleucémique mégacaryocytaire: Contribution à l'étude des syndromes hépato-spléniques, Ann. de méd. **35**:5 (Jan.) 1934; abstracted, J. de méd. de Lyon **14**:753 (Dec. 20) 1933. Mettier, S. R., and Rusk, G. Y.: Fibrosis of the Bone Marrow Associated with a Leukemoid Blood Picture, Am. J. Path. **13**:377 (May) 1937. Carpenter, G., and Flory, C. M.: Chronic Non-Leukemic Myelosis, Arch. Int. Med. **67**:489 (March) 1941. Hickling, R. A.: Chronic Non-Leukemic Myelosis, Quart. J. Med. **6**:253 (July) 1937.

24. Vaughan, J., and Harrison, G. V.: Leuco-Erythroblastic Anemia and Myelosclerosis, J. Path. & Bact. **48**:339 (March) 1939.

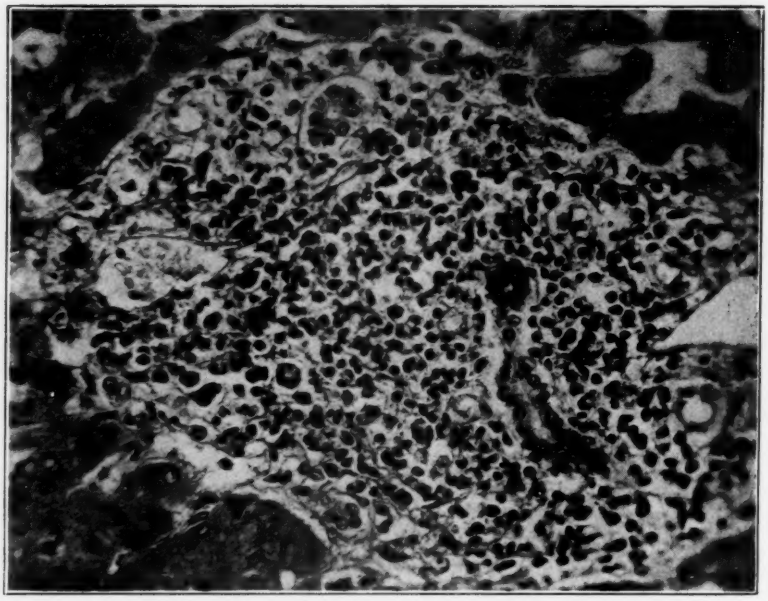

Fig. 1.—Photomicrograph of the liver, showing infiltrations into the periportal spaces with leukemic cells and megakaryocytes. × 180.

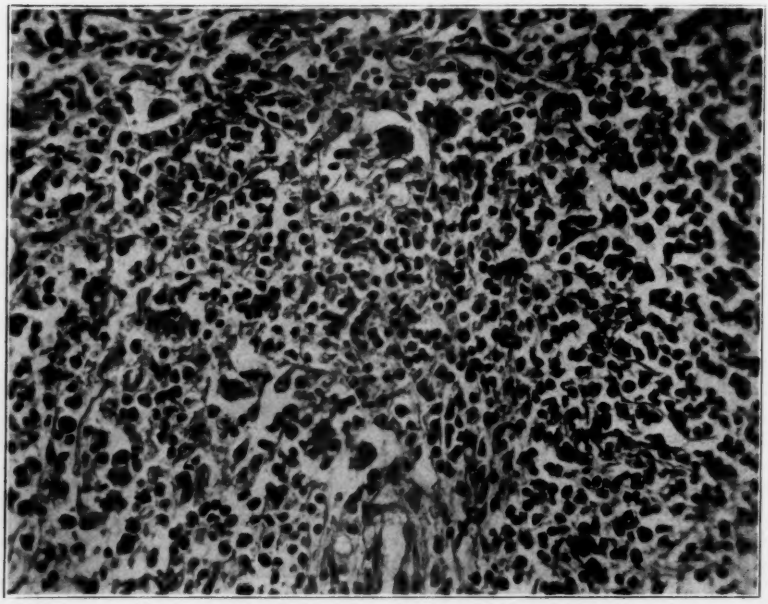

Fig. 2.—Photomicrograph of the spleen. The sinuses are dilated and contain numerous megakaryocites, immature myeloid cells and erythroid cells. × 180.

TABLE 1.—*Blood Counts of a Patient with Megakaryocytic Leukemia*

Date	Red Blood Cell Count	Hemoglobin, %	White Blood Cell Count	Blastocytes	Promyelocytes	Myelocytes	Metamyelocytes	Neutrophilic Nonfilaments	Neutrophilic Filaments	Eosinophils	Basophils	Lymphocytes	Monocytes	Unclassified	Megaloblasts	Early Erythrocytes	Late Erythrocytes	Normoblasts	Comments
First admission																			
2/24/41	3,840,000	69	20,950	..	..	..	..	..	76	..	..	23	1	..	..	..	..	..	Coagulation time, 3 min.
2/25/41	4,230,000	62	15,980	..	..	..	..	..	89	1	..	9	1	..	..	..	..	..	
3/ 1/41	3,810,000	66	10,500	..	..	..	..	..	72	2	1	22	3	..	..	..	..	..	
Second admission																			
1/27/43	4,750,000	..	21,600	..	..	..	..	45	33	..	..	12	10	..	..	..	..	..	Coagulation time, 4½ min.
2/19/43	4,650,000	90	9,800	..	..	..	..	..	60	..	..	30	1	..	..	..	..	..	
7/ 2/46	2,300,000	68	6,000	..	..	..	..	..	50	3	..	45	2	..	..	..	..	..	Slight achromasia
8/13/46	2,980,000	70	.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
8/16/46	2,130,000	55	.....	..	..	1	..	..	65	15	..	20	..	..	..	..	..	Occasional	Achromasia and polychromasia; occasional macrocytes
8/23/46	2,320,000	62	3,950	..	..	..	..	..	47	2	..	50	..	..	..	..	..	8	Same as above
9/ 3/46	3,480,000	70	4,850	..	..	1	..	..	44	2	2	48	2	..	..	..	..	..	Achromasia and polychromasia
10/ 1/46	2,810,000	75	.....	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
10/ 8/46	2,400,000	68	4,850	..	..	2	..	..	32	7	..	58	..	..	..	..	..	7	Anisocytosis, polychromasia and poikilocytosis
Third admission																			
11/ 3/46	2,250,000	44, or 7 Gm.	6,350	16	12	14	10	11	10	5	..	..	..	2	3	3	12	11	Coagulation time, 3¼ min.; bleeding time, 3 min.; diffuse basophilia
11/ 6/46	2,550,000	47, or 7.4 Gm.	5,146	17	8	Eosinophils, 1; neutrophils 3	Neutrophils 6.5; Eosinophils 1	Neutrophils 6.5; Eosinophils 13	9	11	0.6	21	0.4	2	2	7	10	10	Total eosinophils, 26%; marked regeneration of red blood cells
11/11/46	3,310,000	60	6,100	12	3	5	5	15	15	19	..	21	1	..	4	8	3	6	Platelets, 82,000
11/14/46	1,930,000	31.9	5,900	19	6	2	2	1	1	19	1	40	1	7	3	1	2	1	Platelets, 78,000
11/16/46	1,520,000	24	6,438	24	4	6	1	5	2	21	..	35	1	6	3	5	3	7	

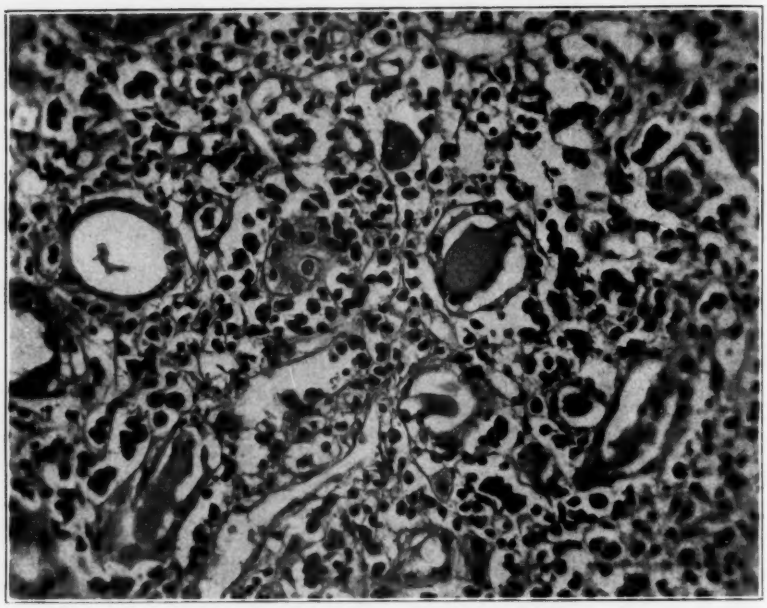

Fig. 3.—Photomicrograph of the kidney, showing numerous megakaryocytes and leukemic infiltrations into the parenchyma. × 180.

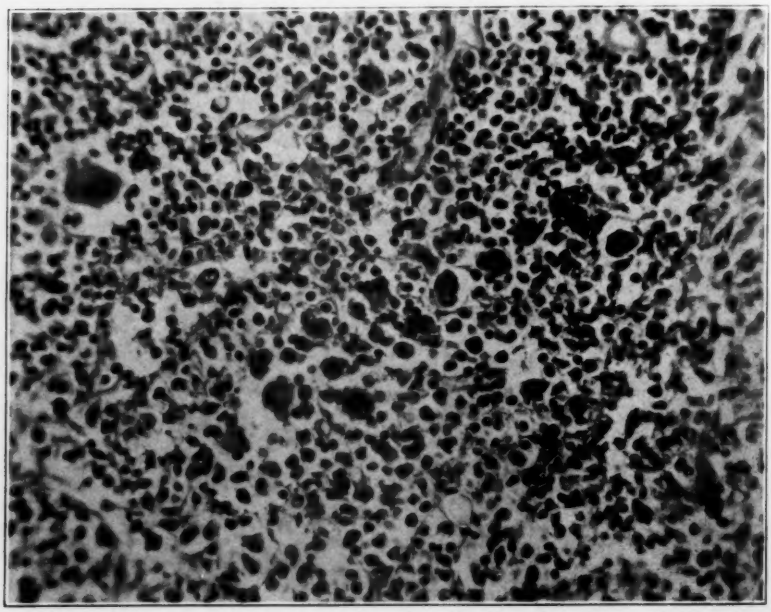

Fig. 4.—Photomicrograph of a lymph node. The architecture has been distorted with numerous megakaryocites, myeloblasts and megaloblasts. × 180.

at this time was essentially normal except for limited motion of the neck on all rotary movements. Roentgenographic studies of the cervical region of the spine revealed advanced cervical arthritic changes, with extreme lipping, bridging and narrowing of the cartilages. He was treated with diathermy, massage and salicylates, and the pain subsided.

He returned to the clinic in July 1946, complaining of easy fatigability, some shortness of breath on exertion and nocturia. The pain in his neck had greatly improved. The positive findings on physical examination at this time were slight limitation of the movements of the neck, a systolic murmur at the apex of the heart, a palpable liver enlarged about 2 fingerbreadths below the costal margin and a moderately enlarged but soft prostate gland. Laboratory procedures revealed moderate anemia. Urinalysis, serologic tests and determination of the nonprotein nitrogen content gave normal results. He was given liver extract and folic acid, which produced a slight change in the blood picture during August and September (table 1). The gastrointestinal tract was essentially normal except for a few diverticula in the sigmoid colon. An orthocardiogram demonstrated calcification of the aortic commissure and slight hypertrophy of the left ventricle. The electrocardiogram was normal.

On Nov. 3, 1946, signs and symptoms of acute myocardial failure developed. At this time the patient was readmitted to the hospital. Physical examination revealed a well developed, well nourished, pale man, 66 years of age, with extreme orthopnea and evidence of peripheral edema. His blood pressure was 146 systolic and 76 diastolic, the temperature 99 F., the pulse rate 72 and regular and the respirations 16. The head was normal except for notable pallor of the conjunctiva and buccal mucosa. The neck was normal except for evidence of increased venous pressure. There was no lymphadenopathy in the neck or in the axillary or inguinal regions. The chest was emphysematous. Auscultation revealed fine crepitant rales at the bases of both lungs. The heart was enlarged to both the right and the left, the apex being 2 cm. beyond the midclavicular line. A loud systolic murmur was heard over the mitral area. The rhythm was regular. The liver was enlarged 2 fingerbreadths below the costal margin in the midclavicular line. The spleen was not palpable. There was moderate pitting edema of both ankles. The reflexes were normal, as were the external genitalia. The prostate gland was moderately enlarged and soft.

Special Studies.—The blood counts are recorded in table 1. On the patient's admission to the hospital the total number of erythrocytes was 2,250,000 per cubic millimeter. The hemoglobin content was 7 Gm. per hundred cubic centimeters. The leukocyte count was 6,350 per cubic millimeter. The differential count was as follows: blastocytes, 16 per cent; promyelocytes, 12 per cent; metamyelocytes, 10 per cent; neutrophilic nonfilaments, 11 per cent; neutrophilic filaments, 10 per cent, and unclassified cells, 2 per cent. There was notable regeneration of the erythrocytes, including 3 megaloblasts, 12 late erythroblasts and 11 normoblasts. Ovalocytes, tailed forms, Howell-Jolly bodies and polychromatophilia were present. At this time a diagnosis of aleukemic myeloid leukemia was made.

Studies of sternal bone marrow obtained by needle aspiration five days after the patient's admission showed increased cellularity, involving all myeloid elements, megakaryocytes and erythroid series. The differential count of the marrow cells is given in table 2. The myelogenic erythrogenic ratio was 2 to 3. There was a relative decrease in the myeloid elements and an absolute increase in the erythroid elements, with eosinophilia. The most bizarre changes were in the early megakaryocytes. They were readily found, and immature forms predominated. Of 100

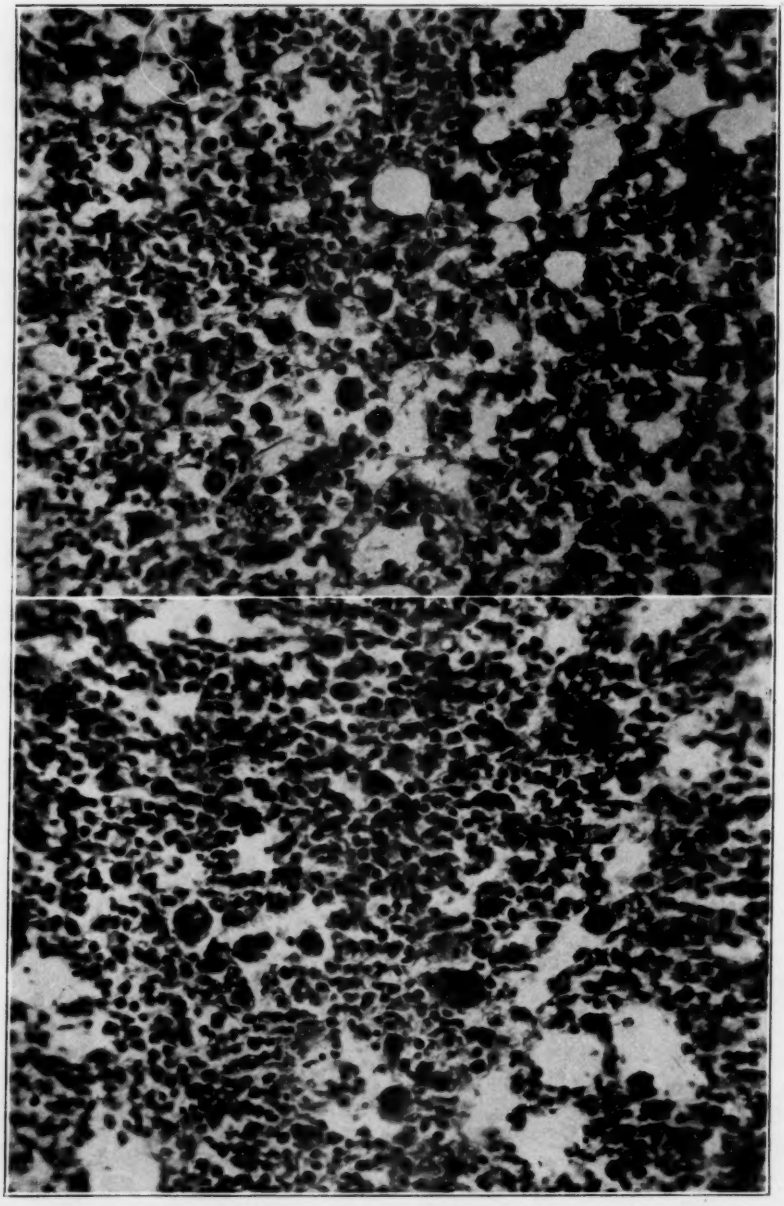

Fig. 5.—Photomicrographs of the sternum (upper figure) and ribs (lower figure), showing hyperplasia of all elements, especially the megakaryocytes. × 180.

megakaryocytes, 72 per cent were early forms, 20 per cent were intermediate forms and 8 per cent were mature forms.

Slides of the peripheral blood and bone marrow were submitted to Dr. L. W. Diggs,[25] of the Cleveland Clinic Foundation, who suggested "the possibility of megakaryocytic leukemia as a suitable term for this picture if supported by further evidence of metastatic giant cells in other viscera"; this opinion was later confirmed. Dr. Verne Mason,[26] of the University of Southern California, and Dr. John H. Lawrence,[27] of the University of California, concurred with the opinion that the case presented many unusual features. Mason described it as "atypical myeloblastic leukemia with an eosinophilic response—a very rare type of leukemia," while Lawrence suggested that it be classified as "atypical myeloid leukemia, megakaryocytic type."

Roentgenograms were made on various occasions from 1941 to 1946. At no time were there demonstrable changes in the architecture of the bones except for advanced degenerative arthritic changes, with extreme lipping, bridging and narrowing of the cartilages of the cervical region of the spine. Gastrointestinal studies in August 1946 were noncontributory. The results of electrocardiographic studies made in 1941 and 1946 were within normal limits, and reactions to serologic tests

TABLE 2.—*Differential Count of the Bone Marrow Cells*

Early nucleus without cytoplasm	2.4	Plasma cells	0.2
Stem cells—undifferentiated	6.4	Monocytes	0.6
Promyelocytes	3.8	Reticuloendothelial cells	4.6
Eosinophilic myelocytes	8.6	Megakaryocytes	1.4
Eosinophilic metamyelocytes	4.4	Mitotic figures	0.4
Eosinophilic nonfilaments	2.2	Megaloblasts	2.2
Eosinophilic filaments	3.6	Early erythroblasts	8.0
Neutrophilic metamyelocytes	1.0	Late erythroblasts	19.8
Neutrophilic nonfilaments	0	Normoblasts	21.6
Neutrophilic filaments	0.2	Mitotic figures	2.8
Lymphocytes	2.8		

were repeatedly negative from 1937. The patient's blood was type B-III, Rh negative.

The nonprotein nitrogen content on July 24, 1946, was 36.5 mg. (not fasting). The fasting levels on November 11 and 13 were 70.5 and 63.2 mg. respectively. The urea nitrogen on November 16 was 42.8 mg. per hundred cubic centimeters of blood. The prothrombin time (Quick's method), taken on November 11, was 96 per cent normal. On November 13 the bleeding time was two minutes and the coagulation time was three to four minutes.

The urine was consistently normal until the patient's terminal illness. On November 6 the specific gravity was 1.018, the reaction was alkaline, traces of sugar and of albumin were present and microscopic examination showed occasional hyaline casts, with 2 to 5 leukocytes per high power field. On November 16 the specific gravity was 1.014, the reaction was acid, albumin was present (3 plus) and numerous coarsely granular casts were present.

Course in Hospital.—Treatment at the time of the patient's admission to the hospital was for acute myocardial failure and consisted of morphine as needed,

25. Diggs, L. W.: Personal communication to the authors.
26. Mason, V. R.: Personal communication to the authors.
27. Lawrence, J. H.: Personal communication to the authors.

meralluride, oxygen, lanatoside C and digitalis. The acute phase of myocardial failure subsided. Two days after his admission, his temperature ranged from 99.6 to 102.8 F.; the pulse rate varied from 100 to 140 per minute, and the respirations were 20 to 30 per minute. For this penicillin therapy was added. He was also treated further with liver extract, folic acid, two citrated whole blood transfusions and one transfusion of red blood cells. The course was progressively downward. On the eighth day in the hospital he became disoriented and petechiae appeared over the body. At this time there was tenderness over the splenic area, and the spleen was first palpated. On November 18 a massive gastrointestinal hemorrhage occurred and the patient died, on the fifteenth day in the hospital.

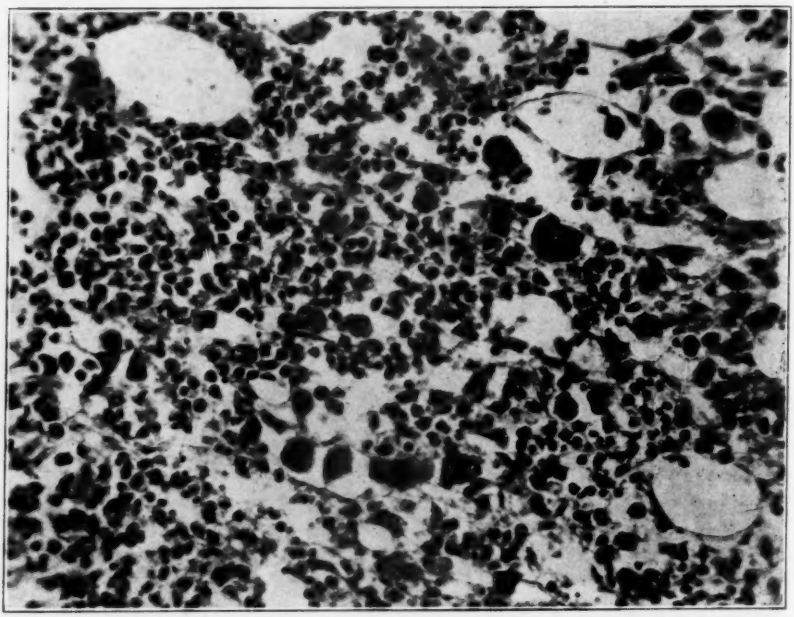

Fig. 6.—Photomicrograph of the vertebrae, showing hyperplasia of all elements, especially the megakaryocytes. × 180.

Observations at Necropsy.—A necropsy was performed four and a half hours after death. The body was that of a well developed, fairly well nourished white man, 66 years of age. The head was of normal contour, and the scalp was covered with thin, receding gray hair. The nares were covered wtih clotted blood and encrusted herpes. The conjunctiva and buccal mucosa were pale. There was no lymphadenopathy in the neck or in the axillary or inguinal areas. There were numerous petechial hemorrhages over the back and shoulders. The subcutaneous fat was a bright lemon yellow color. There was no free fluid in the peritoneal cavity.

Thorax: Each pleural cavity contained approximately 50 cc. of clear, straw-colored fluid. The pericardial sac contained approximately 20 cc. of similar fluid.

Heart: The heart weighed 300 Gm. The aortic, pulmonary and tricuspid valve leaflets were essentially normal. The mitral valve was markedly insufficient, and the leaflets were rolled and thickened, with calcification of the entire ring.

Lungs, Liver and Spleen: The lungs were similar in appearance. They were mottled grayish pink. In the lower lobe of the left lung there were a few elevated, circumscribed areas, which were of a darker red. The mucosa of the bronchi was slightly hyperemic. The liver weighed 1,690 Gm. It was slightly nodular, and the capsule was smooth. A cut section showed a yellowish brown surface, slightly firmer than normal. The spleen weighed 190 Gm. It was soft, and on section the malpighian corpuscles were prominent.

Genitourinary System: The kidneys were similar in appearance. They weighed 130 Gm. each. On section the capsule stripped with a moderate degree of ease, leaving a coarsely granular, mottled grayish and red surface. The cortex was slightly narrowed, the papillae were indistinct and there was an increase in pelvic fat. The ureters and the urinary bladder were normal. The prostate was slightly enlarged and soft.

Gastrointestinal Tract: The mucosa of the stomach showed a few petechiae near the pylorus. The mucosa of the duodenum and jejunum was hyperemic. The ileum contained dark red blood clots. Peyer's patches were prominent, and there were hemorrhagic areas scattered throughout the ileum. The lumen of the cecum and remaining portion of the intestinal tract contained dark brownish bloody exudate. There were a few slightly enlarged lymph nodes scattered throughout the mesentery.

Sections of bone marrow from the ribs, sternum and vertebrae were dark red and hyperplastic. The bone marrow from the femur appeared to be composed of a yellow fat.

Microscopic Study.—Lungs: There were focal areas of fibrosis. In areas the alveoli contained fibrin and polymorphonuclear leukocytes. Other areas were infiltrated with cells, embryonal in character, and numerous giant cells, megakaryocytic in type. Some of the giant cells were multinucleated, others were in mitoses and in many the nuclei were Y-shaped and atypical.

Liver (fig. 1): There was infiltration in the periportal spaces with immature myeloid cells, and giant cells were frequent.

Spleen (fig. 2): The architecture of the spleen was distorted. There were islands of extramedullary hematopoiesis. The pulp and sinusoids were filled with immature myeloid cells and giant cells. Macrophages containing a light brown pigment were numerous. There was also similar pigment outside the cells in the connective tissue.

Kidneys (fig. 3): In the parenchyma there were focal areas of fibrosis, infiltrated with numerous immature myeloid cells and giant cells.

Prostate: This showed an increase in the number of glands with hyperplasia of lining epithelium.

Gastrointestinal Tract: There was infiltration in the mucosa with immature blood cells and giant cells. Hemosiderin pigment was also present.

Mesenteric Lymph Nodes (fig. 4): The architecture was distorted, and immature blood cells and megakaryocytes were numerous.

Bone Marrow (figs. 5 and 6): Sections from the sternum, ribs and vertebrae showed essentially the same picture. There was hyperplasia of all elements, especially of the megakaryocytes, varying from 8 to 15 per low power field. Many were atypical. Mitotic figures were frequent. Sections from the femur showed marrow composed of fat.

Histologic Diagnosis.—The histologic diagnosis was acute megakaryocytic leukemia, with leukemic infiltrations and megakaryocytes in the kidneys, liver, spleen, lymph nodes, lungs and intestines and in the bone marrow of the sternum, ribs and vertebrae.

COMMENT

The general interest today in leukemia is made evident by the following statistics, taken from the report of Sacks and Seeman.[28] Each year since 1940 more than 5,000 persons in the United States have died of leukemia. Dameshek [29] has expressed the belief that in many instances disorders formerly called anemia and purpura were doubtless leukemia but that these are now being accurately diagnosed. There are probably many atypical cases of leukemia that have been missed or erroneously diagnosed or that have remained unreported because they failed to meet the present criteria set forth in current textbooks. The report given here is a case in point. The patient had a leukemia of unusual type, and after careful consideration of the clinical, hematologic and pathologic studies, it is our belief that this is a true "acute megakaryocytic leukemia." It is apparent that the nosologic system should be revised to include megakaryocytic leukemia as a definite clinical entity.

SUMMARY

The salient observations in the case reported were as follows:

In a 66 year old white man who had been observed and studied carefully over a period of years there developed an acute atypical leukemia without apparent splenomegaly or lymphadenopathy. Smears of peripheral blood revealed the presence of aleukemic myeloid leukemia. Aspiration of sternal bone marrow revealed erythromyelomegakaryocytic hyperplasia. No evidence of osteosclerosis or osteofibrosis was present in the roentgenographs or demonstrated at autopsy. Observations at necropsy demonstrated leukemic infiltrations in the viscera. Megakaryocytes were prominent in the lymph nodes, lungs, liver, spleen and kidneys and in the bone marrow of the sternum, ribs and vertebrae.

The paucity of criteria for the diagnosis of megakaryocytic leukemia in the American literature has prompted us to report this case.

28. Sacks, M. S., and Seeman, I. S.: A Statistical Study of Mortality from Leukemia, Blood **2**:1-15 (Jan.) 1947.

29. Dameshek, W.: Is Leukemia Increasing? editorial, Blood **2**:101 (Jan.) 1947.

Progress in Internal Medicine

SYPHILIS

A Review of the Recent Literature

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AND
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(Concluded from Page 840)

TOXIC REACTIONS TO PENICILLIN

Penicillin has become a valuable adjunct in modern syphilology largely because it is, in comparison to other forms of therapy, relatively nontoxic. Such reactions as do occur have been largely restricted to allergic manifestations and are most often dermal sensitizations. No deaths have been attributed to penicillin therapy, and there have been few serious reactions.

In an experience with more than 5,000 patients treated with penicillin in an army hospital. Mendell and Prose [209] encountered six allergic reactions of such severity that it became necessary to discontinue administration of the drug. Four of these reactions occurred early in the course of therapy, with severe pruritis, erythema and urticaria; two were delayed and simulated serum sickness. Testing for sensitivity to penicillin before administration was found to be neither reliable nor practicable.

An extensive review of the toxic reactions accompanying penicillin therapy has been made by Morginson,[210] who has grouped and discussed reactions to penicillin according to its role as (1) direct toxin and primary irritant, (2) antigen and (3) excitant of therapeutic shock and its indirect action on pathologic processes. Penicillin exerts a negligible action as a direct toxin or primary irritant, except after its intrathecal use. With the latter, reactions (convulsions, meningismus and shocklike state) apparently are due to direct irritative phenomena. There is ample evidence that penicillin possesses antigenic and allergenic properties, although the reactions which result are less frequent with purified preparations. Sensitization attributes of commercial penicillin

209. Mendell, T. H., and Prose, P. H.: Severe Allergic Reactions to Penicillin, Am. J. M. Sc. **212**:541 (Nov.) 1946.

210. Morginson, W. J.: Toxic Reaction Accompanying Penicillin Therapy, J. A. M. A. **132**:915 (Dec. 14) 1946.

have been demonstrated by positive reactions to patch and intradermal tests, by indirect or passive transfer tests, by precipitin reactions and, in guinea pigs, by Schultz-Dale tests. Sensitivity may be manifested as immediate or delayed reactions. Immediate reactions usually occur in patients who are known to be sensitive to penicillin or who have had previous doses of the drug, although a few persons appear to have a primary sensitivity. Delayed or acquired sensitization may be produced by repeated injections of penicillin and may be of short duration or persist for years. The allergic symptoms following penicillin therapy usually are benign, of low incidence and transient in nature. Therapeutic shock (Jarisch-Herxheimer reaction) incident to the use of penicillin in the therapy of syphilis is frequently encountered. Temporarily intensified local tissue reactions and systemic manifestations occur. An indirect action on pathologic processes in the form of the so-called therapeutic paradox has been postulated.

Fromer [211] classifies the reactions from penicillin used in the treatment of syphilis as: (1) those due directly to penicillin, which are subdivided into (*a*) early treatment pruritis, i. e., usually a mild generalized itching and dryness of the skin, occasionally with a transient erythema which is not aggravated by continuing penicillin therapy, (*b*) dermatophytid reactions, occurring in patients with preexisting dermatophytoses and (*c*) post-treatment urticaria and serum-sickness-like reactions, and (2) Herxheimer reactions, which were observed in approximately 90 per cent of the patients with early syphilis treated.

Allergic Dermatoses.—Bauer [212] describes three types of allergic dermatoses complicating penicillin therapy: (1) urticaria, the most frequent reaction, (2) erythematovesicular eruptions, usually occurring within twenty-four hours after penicillin is administered intramuscularly and (3) contact dermatitis from local application. All three reactions are of the acquired type. The degree of individual susceptibility, the degree of contact and the period of exposure are all variable factors which combine to determine the severity of the dermatitis. The mechanism underlying the erythematovesicular reactions to penicillin is considered to be analagous to that producing dermatophytids. Cutaneous tests were of only limited value in the diagnosis of any of the three types of penicillin dermatoses discussed.

Callaway and Barefoot [213] have studied hypersensitivity to sodium penicillin and circulating antibodies by means of intracutaneous, passive

211. Fromer, S.: Reactions in the Treatment of Syphilis with Penicillin, Arch. Dermat. & Syph. **55**:385 (March) 1947.

212. Bauer, G. H.: Allergic Dermatoses Complicating Penicillin Therapy, Arch. Dermat. & Syph. **54**:292 (Sept.) 1946.

213. Callaway, J. L., and Barefoot, S. W.: Immunological Studies on Patients Developing Urticaria Associated with Penicillin Therapy, J. Invest. Dermat. **7**:285 (Dec.) 1946.

transfer and precipitin tests in 5 patients in whom urticaria developed in association with penicillin therapy. Reactions to all intracutaneous and passive transfer tests were negative, and the results of precipitin tests were inconclusive.

Allergic sensitivity reactions were demonstrated by Chu and Cutting [214] in guinea pigs and rabbits with pure crystalline penicillin G and with commercial penicillin. These included mild local urticaria after intradermal injections and lesions characteristic of the Arthus phenomenon. Systemic sensitivity was less notable with the crystalline preparation. It is concluded that the purest obtainable crystalline penicillin can act as a sensitizing agent and that the skin bears the brunt of the allergic reaction.

The Treatment of Penicillin Urticaria.—The most frequently encountered reaction to penicillin administered parenterally is urticaria. The experience of Pillsbury, Steiger and Gibson [215] indicates that (1) urticarial reactions are more frequent in patients who have had repeated courses of the drug; (2) some patients in whom urticaria has developed after penicillin therapy may tolerate further use of the drug, whereas others may not; (3) cutaneous tests with penicillin are unreliable as a means of predicting the recurrence of reactions on further administration of penicillin; (4) urticarial reactions may be persistent and severe, and (5) antihistaminic compounds, such as "benadryl hydrochloride" (beta-dimethylaminoethyl benzohydryl ether hydrochloride) [216] and "pyribenzamine hydrochloride" (N′ pyridyl-N′ benzyl-N-dimethylethylenediamine hydrochloride [217]) are useful in controlling penicillin urticaria.

These authors recommend that when urticarial reactions to penicillin occur injections of the drug be suspended and antihistaminic substances administered by mouth. If the urticaria promptly subsides, a test dose of 1,000 units of another manufacturer's penicillin may be administered, and if no untoward reaction occurs, the dosage should be gradually increased until therapeutic levels are reached. The dosage of antihistaminic substances may gradually be reduced, but if evidences of recurrent sensitivity reactions become evident, "benadryl hydrochloride" or "pyribenzamine hydrochloride" should again be given in full therapeutic doses.

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214. Chu, W. C., and Cutting, W. C.: Allergic Sensitization to Penicillin: Experimental Results, Proc. Soc. Exper. Biol. & Med. **63**:347 (Nov.) 1946.

215. Pillsbury, D. M.; Steiger, H. P., and Gibson, T. E.: The Management of Urticaria Due to Penicillin, J. A. M. A. **133**:1255 (April 26) 1947.

216. Distributed by Parke, Davis & Company.

217. Distributed by Ciba Pharmaceutical Products, Inc.

An excellent and comprehensive review of the use of newer antihistaminic agents has been made by Feinberg.[218] In the treatment of allergic reactions to the administration of penicillin, favorable reports from the use of "benadryl hydrochloride" recently have been made by Callaway and Barefoot [213] and by Willcox,[219] and beneficial effects from the use of "pyribenzamine hydrochloride" have been observed by Kampmeier [229] and by Feinberg and Friedlander.[221]

Serum-Sickness-Like Reactions.—Reactions of the serum sickness type following the parenteral administration of penicillin are well known. Gordon [222] and Eisenstadt [223] again describe this type of reaction. Dressler and Dwork [224] have used procaine hydrochloride by intravenous drip in the treatment of the serum-sickness-like type of reaction to penicillin and report favorable results from it.

Anaphylactic Shock.—O'Donovan and Klorfajn [225] report the occurrence of anaphylactic shock following the intramuscular injection of penicillin in a patient who had been sensitized by the use of penicillin spray two months previously.

Febrile Reactions.—DeGennes and his co-workers [226] describe, in addition to reactions to penicillin of the erythroderma and the serum-sickness-like type, a febrile reaction which they attribute to the penicillin. In 2 patients high fever persisted despite clinical evidences of disappearance of the acute infection for which the penicillin had been given. When administration of penicillin was discontinued the fever promptly disappeared. The febrile reactions were noted during a period when a new lot of penicillin was being used, and the authors suspect pyrogenic impurities as the cause.

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218. Feinberg, S. M.: Histamine and Antihistaminic Agents, J. A. M. A. **132**:702 (Nov. 23) 1946.

219. Willcox, R. R.: Use of "Benadryl" for Penicillin Urticaria, Brit. M. J. **2**:732 (Nov. 16) 1946.

220. Kampmeier, R. H.: The Use of Pyribenzamine Hydrochloride in Controlling Urticaria Due to Penicillin, Am. J. Syph., Gonor. & Ven. Dis. **31**:57 (Jan.) 1947.

221. Feinberg, S. M., and Friedlander, S.: Histamine Autogonists: IV. Pyridil-N' Benzyl-N-Dimethylethylenadiamine (Pyribenzamine) in Symptomatic Treatment of Allergic Manifestations, Am. J. M. Sc. **213**:58 (Jan.) 1947.

222. Gordon, E. J.: Delayed Serum Sickness Reaction to Penicillin, J. A. M. A. **131**:727 (June 29) 1946.

223. Eisenstadt, W. S.: Hypersensitivity to Penicillin Simulating Serum Sickness, Minnesota Med. **29**:689 (July) 1946.

224. Dressler, S., and Dwork, R. E.: Reactions to Penicillin: Procaine Hydrochloride Intravenously in the Treatment of Reactions Similar to Serum Sickness, J. A. M. A. **133**:849 (March 22) 1947.

225. O'Donovan, W. J., and Klorfajn, I.: Sensitivity to Penicillin: Anaphylaxis and Desensitization, Lancet **2**:444 (Sept. 28) 1946.

226. deGennes, L.; Bricaire, H.; Laroche, C., and Nelhil, J.: Les accidents d'intolérance a la pénicilline, Presse méd. **55**:161 (March 8) 1947.

Exfoliative Dermatitis.—Nolan and Pedigo [227] report that in a patient who had had urticaria during one course of penicillin exfoliative dermatitis developed when a second course of the drug was given fourteen days after the first had been stopped. They suggest that this reaction was due to some impurity in the penicillin used, since reactions to patch tests were positive with the batch of penicillin that had been administered but not with a different brand of the drug.

Agranulocytosis.—Spain and Clark [228] have observed a patient in whom a generalized erythematous macular rash developed, followed by leukopenia and agranulocytosis, during penicillin therapy. There had been other medications (opiates, barbiturates, physostigmine and vitamins K and C); the use of most of these was continued during the agranulocytosis and given afterward without any effect on the white blood cell count. The appearance of the agranulocytosis in association with a cutaneous rash together with a rise in the white blood cell count soon after administration of penicillin was discontinued suggests that the agranulocytosis probably was due to penicillin.

Purpura.—Anderson [229] reports on a patient in whom, during therapy with penicillin, purpura developed, there being present the symptoms in the joints described by Schönlein and the intestinal crises described by Henoch. Associated with this was a persistent toxic nephritis.

Jaundice.—During recent years, increasing numbers of cases have been reported in which infective hepatitis has been conveyed to patients by means of an infected injection. Hughes [230] reports a series of cases of jaundice following injections of penicillin and considers the condition to have been transmitted from patient to patient by means of contaminated syringes. Evidence is presented to show that a single intramuscular injection of 1 cc. of fluid may lead to contamination of the syringe used.

Thromboplastic Action.—The report of Moldavsky, Hasselbrock and Cateno [231] to the effect that penicillin shortens the coagulation time and decreases the bleeding time of normal blood has stimulated others to study the problem.

227. Nolan, D. E., and Pedigo, G. W.: Exfoliative Dermatitis Following Penicillin Therapy, Ann. Int. Med. **25**:725 (Oct.) 1946.

228. Spain, D. M., and Clark, T. B.: A Case of Agranulocytosis Occurring During the Course of Penicillin Therapy, Ann. Int. Med. **25**:732 (Oct.) 1946.

229. Anderson, A. B.: Anaphylactic Purpura Following Intramuscular Penicillin Therapy, M. J. Australia **1**:305 (March 8) 1947.

230. Hughes, R. R.: Post Penicillin Jaundice, Brit. M. J. **2**:685 (Nov. 9) 1946.

231. Moldavsky, L. F.; Hasselbrock, W. B., and Cateno, C.: Studies in Mechanisms of Penicillin Action: I. Penicillin Effects on Blood Coagulation, Science **102**:38 (July 13) 1945.

Macht [232] expresses the belief that next to its chemotherapeutic properties and low toxicity the most important pharmacologic attribute of penicillin is its thromboplastic activity. The investigator found that amorphous penicillin produced acceleration of the blood-clotting time, an effect that usually persisted for several hours. Comparing various penicillin fractions, he found penicillin X most potent in thromboplastic activity and, in descending order, penicillins K, G, and F to be of lesser potency.

In contrast, Lewis [233] reports that he was unable to demonstrate any in vitro or in vivo effect of penicillin on the coagulation of blood. No significant changes were observed in coagulation time, clot retraction, prothrombin concentration, fibrinogen concentration, platelet count or bleeding time in normal or hemophilic subjects.

Whichever of these two conclusions may be correct, thrombotic accidents in medical practice after the use of penicillin are extremely rare.

Changes in Viscosity of the Blood.—Loiseleur, Levy and Sureau [234] report transitory increases in the viscosity of the blood serum during administration of penicillin, which disappear rapidly after the termination of treatment. With amorphous penicillin the change was more striking than with crystalline penicillin. Since the viscosity of the penicillin solutions was less than that of serum itself, it is hypothesized that the increase in viscosity results from the formation of a specific antibody. The authors suggest further that the "antibody" which they have hypothesized may be concerned in some way with the sensitization reactions provoked by penicillin.

Effects of Penicillin on Menstrual Function.—McLachlan and Brown [235] report that alterations in the menstrual cycles occurred in 91.3 per cent of 206 women treated with penicillin in varying time-dose schedules. The most frequent changes were lengthening or shortening of the cycle or duration of flow and the occurrence of dysmenorrhea. Uterine cramps and/or bleeding occurred in 43.8 per cent of 32 women who were treated during pregnancy, and in 1 case it was thought that penicillin was responsible for premature induction of labor. Alterations in the lochia were observed in 12 of 16 women treated during puerperium. Lactation was diminished in

232. Macht, D. I.: Thromboplastic Properties of Penicillin and Streptomycin, Science **105**:313 (March 21) 1947.

233. Lewis, J. H.: Effect of Penicillin on Blood Coagulation, Proc. Soc. Exper. Biol. & Med. **63**:538 (Dec.) 1946.

234. Loiseleur, J.; Levy, M., and Sureau, B.: Sur les réactions sériques consécutives a l'administration de pénicilline, Ann. Inst. Pasteur **72**:931 (Nov.-Dec.) 1946.

235. McLachlan, A. E. W., and Brown, D. D.: Effects of Penicillin Administration on Menstrual and Other Sexual Cycle Functions, Brit. J. Ven. Dis. **23**:1 (March) 1947.

75 per cent of this group of patients, and it is recorded that normal lactation usually returned when the use of penicillin was discontinued. The authors express the belief that these effects of administration of penicillin were due to impurities in the drug since there was a decreasing incidence as purer preparations became available.

Masking of Syphilis by Small Doses of Penicillin.—Physicians interested in the therapy of gonorrhea have recognized that penicillin administered for gonococcic urethritis may be sufficiently spirocheticidal to alter or mask the symptoms of a concomitantly acquired syphilitic infection. It has been suggested that preclinical syphilis may be recognized by the occurrence of febrile reactions of the Jarisch-Herxheimer type occurring after penicillin therapy for gonorrhea. Fromer, Cutler and Levitan [236] confirm these observations and state the belief that although there are exceptions to the rule it is good practice to subject patients in whom there develops a febrile reaction to penicillin therapy for gonorrhea to close scrutiny, both clinical and serologic, for a period of four months after therapy. Within this period additional evidence of incipient syphilis may well be expected to develop.

That penicillin given routinely for a variety of conditions is likely to obscure the early manifestations of syphilis is again stressed by Cronin,[237] who cites 7 cases in which are illustrated the difficulties in the diagnosis of syphilis caused by penicillin medication for other diseases. This author recommends that before penicillin is administered a complete examination be made and that routine serologic tests be performed. He also suggests that the patient's temperature be taken every three hours for the first twelve hours of administration of penicillin, in the belief that any febrile response suggests a Herxheimer reaction from a subclinical infection with syphilis.

Cronin [238] states that "there is no evidence that penicillin in amounts up to 150,000 units delays the appearance of syphilis for more than 3 months after treatment. Unnecessary psychologic trauma and little benefit will accrue in extending surveillance beyond this period." He bases this conclusion on a survey of the available literature together with an analysis of 19 cases in which syphilis was personally observed to develop after penicillin treatment for gonorrhea.

Herxheimer Reactions from Penicillin.—Seeking to avoid the occurrence of Jarisch-Herxheimer reactions by beginning penicillin therapy

236. Fromer, S.; Cutler, J. C., and Levitan, S.: Masking of Early Syphilis by Penicillin Therapy in Gonorrhea, J. Ven. Dis. Inform. **27**:174 (July) 1946.

237. Cronin, E.: "Masked" Syphilis: Dangers of Penicillin Therapy, Lancet **2**:84 (July 20) 1946.

238. Cronin, E.: The Evolution of Syphilis After Small Doses of Penicillin: A Critical Survey, Brit. J. Ven. Dis. **23**:15 (March) 1947.

with small initial doses, Olansky [239] found that even in small doses (1,000 units) the drug evoked in at least 6 patients severe reactions of this type. He concludes that "penicillin, even in small doses, should not be administered to patients with late or complicated syphilis until a course of bismuth has been given." [240]

OTHER ANTIBIOTIC PREPARATIONS IN EXPERIMENTAL SYPHILIS

Streptomycin.—Fiskin and Gruhzit [241] report that the administration of streptomycin to syphilitic rabbits in doses of 1,000 to 4,000 subtilis units per kilogram of weight per day for a period of twenty days produced no regression of lesions or disappearance of spirochetes. Continued administration of streptomycin to the same rabbits in doses of 6,000, 8,000 and 10,000 subtilis units per kilogram per day for an additional thirteen days did not suffice to heal the overt lesions or achieve cure, since 100 per cent of the animals retained viable organisms as demonstrated by lymph node transfers to other animals. The virulence of the strain of Treponema pallidum did not appear to have been altered by the prolonged administration of streptomycin.

Kolmer, Rule and Paul [242] report that streptomycin by intermittent intramuscular injection was slightly but temporarily effective in the treatment of 3 out of 6 rabbits with acute syphilitic orchitis in a total dosage of 24,000 to 240,000 units per kilogram of weight, but complete cures were not observed in any of the animals receiving total dosages of from 24,000 to 240,000 units per kilogram by intramuscular injection over a period of eight days.

Tyrothricin.—Kolmer and Rule [243] report that the administration of tyrothricin intravenously to rabbits with acute testicular syphilomas was completely ineffectual. None of 16 animals showed any healing of the testicular lesions, and in no case did dark field examination fail to reveal the persistence of T. pallidum.

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239. Olansky, S.: The Herxheimer Reactions of Relatively Small Doses of Penicillin, J. Ven. Dis. Inform. **28**:26 (Feb.) 1947.

240. It should be remarked that 4 of this author's 6 patients had early syphilis. The only basis for his conclusion is to be found in a consideration of the patient in his case 3, a 32 year old man with gumma of the testis in whom, shortly after the institution of penicillin treatment, there developed fever and a temporary increase in testicular swelling and tenderness.

241. Fiskin, R. A., and Gruhzit, O. M.: The Effect of Streptomycin on Experimental Syphilis Infections of Rabbits, Am. J. Syph., Gonor. & Ven. Dis. **30**:581 (Nov.) 1946.

242. Kolmer, J. A.; Rule, A. M., and Paul, A. J.: Streptomycin in Treatment of Acute Syphilitic Orchitis of Rabbits, Proc. Soc. Exper. Biol. & Med. **63**:242 (Nov.) 1946.

243. Kolmer, J. A., and Rule, A. M.: Failure of Tyrothricin in the Treatment of Experimental Syphilis of Rabbits, Proc. Soc. Exper. Biol. & Med. **63**:375 (Nov.) 1946.

MALARIA THERAPY

Quantitative Inoculation with Parasites.—The febrile course of inoculation vivax malaria, unlike the naturally acquired infection, rarely is one of tertian periodicity. In the majority of cases of induced infections quotidian cycles are exhibited, with varying degrees of irregularity. The administration of 5 to 10 cc. of malarial blood commonly is followed by a period of continuous remittent fever accompanied with malaise and fatigue, often exhausting the patient prior to the establishment of true malarial paroxysms. This initial period of remittent fever has been thought to be the result of asynchronism of different broods of malaria parasites. This asynchronization of parasites following intravenous inoculation apparently is produced by the injection of a large number of organisms in different stages of schizogony, resulting in remittent fever when clinical levels of parasitemia are reached. Synchronization of these broods occurs only after several days of clinical activity has permitted domination by a single brood and cycle.

Kaplan, Read and Becker [244] have sought to eliminate the disturbing period of remittent fever by controlling the technics of inoculation. Intradermal inoculation was followed by the shortest period of, and the least severe, remittent fever. The occurrence of 18.8 per cent of unsuccessful "takes" with this technic, however, makes the routine use of the method unjustified. Intravenous inoculation with doses ranging from 1,000,000 to 150,000,000 parasites revealed in susceptible patients that the higher the dose the longer the period of remittent fever in a high percentage. The lower the dose the shorter and less severe was the remittent fever, resembling the results following intradermal inoculation. It also was possible to correlate the occurrence of the desirable tertian cycle with the technic of inoculation, for the percentage of patients with tertian cycles after intravenous inoculation varied inversely with the parasite dose. The intravenous inoculation of 1,000,000 Plasmodium vivax parasites (determined by correlating the amount of inoculum with the quantitative parasite count of the donor) is recommended as a standard procedure in the therapy of neurosyphilis when susceptible white patients are being dealt with. This technic eliminated the period of remittent fever for 35.7 per cent and shortened it to two days or less for 67.9 per cent of patients included in the study.

Therapeutic Malaria of Foreign Origin.—Engstrom and his fellow workers [245] inoculated 105 neurosyphilitic patients (172 white and 23

244. Kaplan, L. I.; Read, H. S., and Becker, F. T.: Use of Quantitative Parasite Inoculation Doses in Plasmodium Vivax Malaria Therapy, Arch. Neurol. & Psychiat. **56**:65 (July) 1946.

245. Engstrom, W. W.; Gordon, H. H., and Marble, A.: Induced Malaria of Foreign Origin, Arch. Int. Med. **79**:185 (Feb.) 1947.

Negro) with vivax malaria of Pacific or Mediterranean origin. Their attempts to transfer P. vivax malaria, whether by mosquito bites or by inoculation of blood, were highly successful in white patients whether they gave a past history of malaria or not and relatively unsuccessful in Negroes. Spontaneous remission of fever was observed more than three times as frequently in those who gave a history of having had malaria as in those who did not. It was noted that as the disease progressed the concentration of parasites in the blood at first increased rapidly but after the eleventh day began to fall. Sixty-five per cent of the patients inoculated with mosquitoes infected with Pacific strains of P. vivax had relapses, whereas no patient relapsed who had been inoculated intravenously with blood containing the same strains. Quartan malaria was transmitted to 48 patients (45 Negro and 3 white) by inoculation of blood containing Plasmodium malariae. Quartan infections differed from tertian not only in the longer interval between paroxysms but also in the longer period of incubation, the slower response to quinacrine hydrochloride therapy and the tendency to cause serious renal complications.

Biochemical Studies During Fever Therapy.—The biochemical studies of Gall and Steinberg [246] on patients with malarial and artificial fevers revealed the development of transient hypophosphatemia during the febrile paroxysm. In the search for an explanation for the hypophosphatemia, determinations of the blood glucose levels were made at comparable periods. From these studies it became apparent that the fall in serum phosphorus was attended by a rise in glucose in a manner which suggested an inverse relationship between the two. It was thought that the hyperglycemia resulted from an acceleration of metabolism and the simultaneously increased muscular tonus and that the hypophosphatemia was linked with increased utilization of glucose. Hypophosphatemia presumably was associated with the formation and deposition of hexosephosphate in the tissues. No significant alterations were observed in the serum, calcium, potassium, magnesium, creatine or creatinine levels. The serum protein levels fell slightly during malarial fever but remained unchanged in artificial fever.

Pathologic studies in human and experimental malaria have shown lesions not unlike those occurring in shock. It has been suggested that these lesions resulted from anoxemia produced by the rapid destruction of erythrocytes. It is reported by Rigdon and Varnadoe [247] that the administration of oxygen may be beneficial in severe malarial infections.

246. Gall, E. A., and Steinberg, A.: Biochemical Studies During Malarial and Artificial Fevers, J. Lab. & Clin. Med. **32**:508 (May) 1947.

247. Rigdon, R. H., and Varnadoe, N. B.: Effect of Oxygen on Malaria: An in Vivo Study in Ducks, J. Lab. & Clin. Med. **32**:57 (Jan.) 1947.

The increased amount of oxygen apparently helped to compensate for the decrease in hemoglobin content. Ducks with a severe malarial infection when placed in an oxygen chamber immediately showed considerable clinical improvement and survived for a longer period than those kept at room temperature. This improvement is attributed to the greater amount of oxygen available for transmission to the anoxemic tissues.

Tests of Hepatic Function During Therapeutic Malaria.—Lippincott and his associates [248] have performed tests of hepatic function before, during and after therapy with induced malaria. Although there was evidence of impaired hepatic efficiency in the majority of 138 patients during fever therapy, termination of the therapy resulted in a fairly prompt return to normal, by all indications, of hepatic function. In no case was there any evidence of persistent hepatic damage.

During fever therapy, there occurred in most patients studied retention of sulfobromophthalein, ranging up to 40 per cent. Abnormal values also were observed, during malaria treatment, with the cephalin flocculation test and with the icterus index, serum bilirubin and urobilinogen tests. After the administration of quinacrine hydrochloride, the tendency was for the results in practically all tests to be normal within approximately two months.

Glenn and his co-workers [249] found evidence of impaired hepatic function in all of a group of 60 patients undergoing malarial therapy for neurosyphilis. After termination of the malarial fever, most abnormalities disappeared promptly. The function of detoxification, as measured by the test for hippuric acid excretion, was depressed for the longest period. The degree of hepatomegaly could not be correlated with the severity of hepatic dysfunction. The digestive symptoms experienced during therapeutic malaria appeared not to be due solely to hepatic damage, although anorexia was more frequent as the serum bilirubin level became elevated. The authors could demonstrate no significant protection of the liver by the addition to the diet of protein or vitamins or by injections of crude liver extract. However, the administration of 75 Gm. of dextrose intravenously daily did decrease the incidence of hepatic enlargement.

Jaundice in Malaria.—Hills [250] believes that malarial jaundice is a distinct clinical entity characterized by the abrupt onset of painless icterus

248. Lippincott, S. W.; Marble, A.; Ellerbrook, L. D.; Hesselbrock, W. B.; Engstrom, W. W., and Gordon, H. H.: Liver Function Tests in Neurosyphilitic Patients with Induced Vivax Malaria of Pacific and Mediterranean Origin, J. Lab. & Clin. Med. **31**:991 (Sept.) 1946.

249. Glenn, P. M.; Kaplan, L. I.; Read, H. S., and Becker, F. T.: Clinical and Laboratory Studies of Liver Function in Therapeutic Malaria, Am. J. M. Sc. **212**:197 (Aug.) 1946.

250. Hills, A. G.: Malarial Jaundice, Am. J. M. Sc. **212**:45 (July) 1946.

in a patient febrile with malaria. It is of brief duration, averaging seven days in his experience. Enlargement of the liver and billirubinuria were common. Acholic stools did not occur. Malarial jaundice seemed primarily a hemolytic icterus, but hepatic injury secondary to hemolysis and fever appeared to contribute to the production of the jaundice. There was no evidence that quinine or quinacrine hydrochloride had any part in its pathogenesis.

In this series the forms of disease ranged from minimal hyperbilirubinemia to definite icterus with hemoglobinuria. The author believes that hemoglobinuria is the rule in severe malarial jaundice and that because of its threat to renal function it is a complication to be dreaded. It is concluded that hemoglobinuria will appear in malarial jaundice when hemolysis becomes so intense that the reticuloendothelial system is unable to keep the plasma hemoglobin level below the renal threshold and that the syndrome of blackwater fever may be due solely to unusually severe malarial hemolysis.

Reports such as those of Sartwell [251] and of Ginsburg,[252] both of whom describe cases of hemologous serum hepatitis following blood transfusion, raise the possibility that this condition may occur after inoculation malaria. The reviewers have seen several patients in the past few years who became icteric at intervals after inoculation with malarial blood, comparable to the occurrence described by these authors.

Purpura in Malaria.—Shrager and Kean [253] report that in 10,000 consecutive patients with malaria treated at Gorgas Hospital there were 10 cases (0.1 per cent) in which the condition was complicated by purpura. Purpura occurred in an untreated patient, but in the other 9 cases the purpura followed the use of quinine. The thrombocytopenic and nonthrombocytopenic varieties of the disease occurred in equal proportion. The complication was a serious one, as 4 of the patients were critically ill, and 2 died.

Allergy in Malaria.—Allergic manifestations resulting from the foreign protein in the malarial parasite are medical curiosities. Grazier,[254] who has studied this problem, states that in the few cases described in the literature the allergic phenomena invariably accompanied the onset of fever or appeared immediately preceding it. Allergic manifestations (urticaria) occur at a time when merozoites, being free in the blood stream, make a foreign protein available. The author has observed

251. Sartwell, P. E.: Infectious Hepatitis in Relation to Blood Transfusion, Bull. U. S. Army M. Dept. **7**:90 (Jan.) 1947.

252. Ginsburg, H. S.: Homologous Serum Hepatitis Following Transfusion, Arch. Int. Med. **79**:555 (May) 1947.

253. Shrager, J., and Kean, B. H.: Purpura as a Complication of Malaria, Am. J. M. Sc. **212**:54 (July) 1946.

254. Grazier, H. F.: Allergy in Malaria, Ann. Int. Med. **25**:968 (Dec.) 1946.

approximately 500 cases of malaria, with but 1 instance of specific sensitivity to the malarial parasite, and believes the incidence of allergic phenomena to be even lower than his data suggest.

Thiobismol in Therapeutic Quartan Malaria.—The efficacy of "thiobismol" (sodium bismuth thioglycollate) in reducing the frequency of paroxysms of vivax malaria without eliminating them completely is well known. Injections of this drug, by virtue of its inhibitory effect on half-grown P. vivax parasites, convert the febrile course from quotidian to tertian periodicity and thus facilitate temporary interruptions of malaria and allow a full course of therapy without rapidly exhausting the patient with daily febrile episodes.

In quartan malaria the use of sodium bismuth thioglycollate is less well understood. Kaplan, Read and Becker [255] report that in 42.5 per cent of 38 patients given "thiobismol" injections there was the desired therapeutic effect. The drug was most frequently effective when administered to patients with double quartan or quotidian quartan malaria. Injections of it resulted in appreciable decreases in the parasite count, the effect being on immature parasites. The authors conclude that "thiobismol is an effective drug for reducing the frequency of paroxysms and regulating the febrile cycles in patients experiencing double quartan or quotidian quartan malaria. Its use may enable patients with neurosyphilis to tolerate better complete courses of therapeutic quartan malaria."

Blood Serologic Tests after Malaria Therapy.—Several common clinical concepts relating to dementia paralytica have been challenged by Kirman.[256] Reviewing the clinical records of 312 patients with dementia paralytica and finding a low incidence (3 per cent) of clinical lesions elsewhere in the body, the author concludes that adjuvant metal chemotherapy is unnecessary after therapeutic malaria. In his experience, moreover, persistently positive serologic reactions following malarial therapy were no more common than in other forms of late syphilis.

PROPHYLAXIS OF SYPHILIS

Mercury.—Laug and his co-workers,[257] who have studied the absorption of mercury by cutaneous inunction, find the urinary excretion to be an unsatisfactory indication of the degree to which mercury pene-

255. Kaplan, L. I.; Read, H. S., and Becker, F. T.: The Action of Thiobismol on Therapeutic Quartan Malaria, J. Lab. & Clin. Med. **31**:735 (July) 1946.

256. Kirman, B. H.: Significance of the Blood Wassermann Reaction After Malaria Therapy in General Paralysis, Brit. J. Ven. Dis. **22**:168 (Dec.) 1946.

257. Laug, E. P.; Vos, E. A.; Umberger, E. J., and Kunzi, F. M.: A Method for the Determination of Cutaneous Penetration of Mercury, J. Pharmacol. & Exper. Therap. **89**:42 (Jan.) 1947.

trates the skin. They suggest an experimental method dependent on measurements of the quantity of mercury which is stored in the kidney during twenty-four hours of exposure. Using the storage of mercury in the kidney as a measure of the amount that has passed through the skin, they have found that a number of factors influence the cutaneous penetration of mercury: 1. Covering of the site of inunction increased the penetration of mercury fourfold. 2. The location of the site of inunction appeared not to effect the degree of penetration. 3. Removal of excess ointment from the skin reduced the absorption of mercury. 4. Washing of the skin with soap and water before inunction had little or no influence on penetration. 5. After application to smaller areas of skin mercury was less well absorbed than when applied to larger areas.

These same authors [258] report that the cutaneous absorption of mercury is greatly influenced by the vehicle in which it is suspended. In their experience, oleic acid and propylene glycol supported the greatest penetration of mercury. The least satisfactory vehicles appeared to be those most frequently incorporated in prophylactic ointments. Next to the vehicle, the compound of mercury seemed to have the greatest influence on the cutaneous penetration. The concentration of mercury in the prophylactic ointment affected its absorption but slightly, although a twenty-five fold increase in concentration in the ointment caused a doubling of the amount of penetration. Reduction in the particle size of mild mercurous chloride increased the penetration of mercury significantly. The addition of a 15 per cent solution of sulfathiazole to mild mercurous chloride ointment reduced cutaneous penetration by approximately one third. Generally speaking, it appeared that the type of vehicle, whether fat, water-in-oil or oil-in-water emulsion, is less important to penetration of mercury than the constituents which the ointment contains.

Arsenicals.—A number of amide-substituted phenylarseneoxides have been shown to be actively spirocheticidal in vitro and to be effective prophylactically in experimental rabbit syphilis when applied as a solution in propylene glycol to an inoculated superficial incision on the skin of the back. Eagle, Magnuson and Fleischman [259] have found that these compounds are less effective prophylactically when incorporated in ointments. There was no significant difference between ointments with a fatty base containing a finely divided arsenical in suspension and ointments with a continuous aqueous phase containing

258. Laug, E. P.; Vos, E. A.; Kunzi, F. M., and Umberger, E. J.: A Study of Certain Factors Governing the Penetration of Mercury Through the Skin of the Rat and the Rabbit, J. Pharmacol. & Exper. Therap. **89**:52 (Jan.) 1947.

259. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Local Chemical Prophylaxis of Experimental Syphilis with Phenyl Arsenoxides Incorporated in Ointments and in Soap, Am. J. Syph., Gonor. & Ven. Dis. **31**:257 (May) 1947.

the arsenical in solution. A representative compound (P-arsenosophenoxyacetamide) was active prophylactically when applied as an aqueous solution in dilute soap (5 per cent potassium oleate). The significance of these observations with respect to the prophylaxis of human syphilis is discussed, with particular reference to the possible use of soaps containing stable arsenoxides.

Penicillin.—Eagle, Magnuson and Fleischman [260] have shown that the dosage of penicillin necessary to abort syphilitic infections in rabbits when given four days after inoculation increases progressively with the size of the inoculum. After intracutaneous inoculation with 200,000 spirochetes it required fifteen to fifty times as much penicillin to abort the disease as was necessary with an inoculum of only twenty organisms. It was further demonstrated that with a fixed inoculum of 2,000 spirochetes the curative dose of penicillin increased progressively with the duration of the experimental infection. These data suggest to the authors a new approach to the prophylaxis of syphilis, since syphilitic infection in man may perhaps prove susceptible to abortion with relatively small doses of penicillin, provided these are administered promptly.

CONTROL OF SYPHILIS

In any process as complex as the control of venereal disease significant changes in one aspect of the program may require alterations in other aspects if the program is to be kept in proper balance.

An obvious need, for example, is the development of some means whereby practicing physicians may be kept informed of newer methods of diagnosis and treatment and of the facilities available for their application. Refresher courses, such as those described by Heyman,[261] offer a possible solution. The physician cooperation plan described by Hollister [262] has as its primary purpose the utilization of private physicians in case finding.

Nonetheless, it should be pointed out that however effective may be the newer therapeutic procedures and to whatever degree cooperation of physicians may be attained effective control of venereal disease also necessitates improved case finding and case holding. Some of the newer technics are outlined in a recent issue of the *Journal of Venereal*

260. Eagle, H.; Magnuson, H. J., and Fleischman, R.: Relation of the Size of the Inoculum and the Age of the Infection to the Curative Dose of Penicillin in Experimental Syphilis, with Particular Reference to the Feasibility of its Prophylactic Use, J. Exper. Med. **85**:423 (April) 1947.

261. Heyman, A.: Postgraduate Instruction in Venereal Disease, J. Ven. Dis. Inform. **27**:253 (Oct.) 1946.

262. Hollister, W. G.: Self-Interview Forms in Private Physician Contact Reporting: A New Technic in Case Finding; a Preliminary Report, J. Ven. Dis. Inform. **27**:240 (Oct.) 1946.

Disease Information. Bundesen, Bauer and Baker [263] recommend the use of telegrams as an inexpensive and efficacious (in 46.2 per cent of cases) means of bringing in contacts for examination, at least in urban areas. Koch and Thornton [264] also have found the use of telegrams to be economical and effective in case holding. Rosenthal and Kerchner [265] record that in the New York City Health Department the use of registered letters was successful (20 per cent) in persuading suspected contacts to report for examination.

Clerical Aspects of Control of Syphilis.—Without an adequate clerical system, a program for the control of venereal disease, especially that of a local health unit, cannot function properly. Such a program should be planned in terms of smooth clinical function, accurate reporting of morbidity and avoidance of duplication.

A satisfactory clerical system evolved over a period of years is described by Pariser,[266] who divides clerical functions into three phases, i. e., processing, admission and statistics. For the processing of epidemiologic information, two files are considered desirable, which are a central registry and a pending file. The second function, i. e., admission, which is directly concerned with the operation of clinics, requires an "expected in" file, a chart file subdivided into active and inactive categories and a "delinquent file." The third function, dealing with statistical analyses, necessitates the completion of detailed reports on morbidity.

Control of Syphilis by Quarantine.—Most local health officers are empowered to quarantine patients with infectious venereal disease in order to prevent further spread of infection, but this power seldom is used. Instead, reliance usually is placed on persuasion and education, with the threat of quarantine reserved for the occasional patient who refuses to cooperate.

During World War II, only one state, South Carolina, used its quarantine powers as a routine, statewide and continuing activity. Chisolm [267] reports on the results achieved in the first year (1945) of its operation. There were prompt and significant increases in the

263. Bundesen, H. N.; Bauer, T. J., and Baker, A. H.: Evaluative Study of Three Types of Epidemiologic Activity on Three Hundred and Sixty Syphilis Contacts, J. Ven. Dis. Inform. **27**:244 (Oct.) 1946.

264. Koch, R. A., and Thornton, M.: Use of Telegrams in Venereal Disease Case Holding, J. Ven. Dis. Inform. **27**:246 (Oct.) 1946.

265. Rosenthal, T., and Kerchner, G.: Experiences with Registered Letter Follow-Up in the New York City Health Department, J. Ven. Dis. Inform. **27**: 249 (Oct.) 1946.

266. Pariser, H.: A Proposed Clerical System for a City Venereal Disease Program, Am. J. Syph., Gonor. & Ven. Dis. **31**:181 (March) 1947.

267. Chisolm, J. M.: Control of Syphilis by Quarantine: A State-Wide Quarantine Program for the Control of Infectious Syphilis, Yale J. Biol. & Med. **19**:557 (March) 1947.

number of patients with early syphilis admitted to rapid treatment centers and in the percentage with untreated early syphilis sent to hospitals. Improvement in investigation of contacts is claimed. The local health departments experienced little difficulty in enforcing the quarantine, and there was no record of a patient successfully evading quarantine through court procedures.

Mass Serologic Testing.—Stimulated by the example of other mass blood-testing programs, the Venereal Disease Control Committee of San Antonio, Texas, decided in the autumn of 1945 to promote a citywide campaign against syphilis. Robbins and Green,[268] who were intimately associated with this program, report that the number of cases of infectious syphilis found as a result of this campaign was "not impressive." They report that when reliance is placed on voluntary mass blood testing promiscuous persons cannot be expected to volunteer for testing in large numbers. The extensive health education accomplished by the program is nonetheless considered to be a noteworthy achievement.

Investigation of Contacts.—There has been in recent years an increasing awareness of the importance of efficient case finding in the control of venereal disease. Crowley and Tucker[269] opine that investigation of contacts, if intelligently carried out by competent workers, is one of the most efficacious methods of case finding and one that should take precedence over other technics. In the state of Tennessee the maximum cost of bringing to treatment a single patient with infectious syphilis was $63.93, a figure lower than any yet recorded for any other method of case finding.

There are no infallible rules to be followed by those who undertake case-finding interviews with patients who have infectious syphilis. Steiger and Taylor[270] outline "some of the points which easily can be overlooked but which have been found useful in contact questioning."

Prerequisites for a successful interview include privacy, an understanding and noncritical attitude on the part of the interviewer, a basic knowledge of the venereal diseases and a knowledge of the patient's individual case. It is suggested that the interview be begun by the establishment of a proper degree of rapport and that much can be accomplished by explaining that the patient's own prognosis has been improved as a result of prompt diagnosis. The authors have been impressed with the results of the "community spirit" approach in obtain-

268. Robbins, L. C., and Green, W. S.: Preliminary Report on the San Antonio Blood Test Campaign, J. Ven. Dis. Inform. **27**:196 (Aug.) 1946.

269. Crowley, E. L., and Tucker, C. B.: The Cost of Venereal Disease Contact Investigation in Tennessee, J. Ven. Dis. Inform. **28**:81 (May) 1947.

270. Steiger, H. P., and Taylor, J. B.: Venereal Disease Interviewing, J. Ven. Dis. Inform. **28**:55 (April) 1947.

ing the names of sexual contacts. If the name of the contact is unknown to the patient, a detailed description or the circumstances of exposure may suffice for identification. Whether routine or rapid treatment is given, the consideration of case holding is highly important.

Premarital Serologic Tests for Syphilis.—In the majority of states of the union premarital serologic tests for syphilis are now required by law. It is generally agreed in support of this type of legislation that it has as its primary objective the control of a considerable proportion of the syphilitic infections which are constantly occurring. This objective is said to be attained by (1) finding patients with syphilis, thus leading to their treatment and the prevention of further spread, (2) preventing the infection of the marital partner, (3) preventing the occurrence of congenital syphilis and (4) educating the public about syphilis. Some of the objections to compulsory premarital serologic testing have recently been summarized by Nelson,[271] who states:

> There is no justification for arbitrarily subjecting a part of the general population to blood testing for the purpose of finding cases of syphilis. . . . If mass blood testing is sound, it should be applied to the entire population. . . . Mass blood testing . . . implies that if a person is tested once, the question of his infection with syphilis will be settled for all time. . . . If the *spread* of syphilis is to be prevented by mass blood testing, the infections must be detected *while they are still communicable*. . . . Blood tests would have to be done every few weeks in order to find new infections while they are still communicable. . . . It cost (in Birmingham, Ala.) nearly $1,000 to find a single openly infectious case by this mass blood testing method. . . .
>
> If the marital partner is to be protected, it must be assumed that the couple do not have intercourse prior to marriage, an assumption which is by no means always valid. It must be assumed, also, that a blood test will determine by itself whether or not a person has syphilis. That cannot be assumed. . . . Those persons who are found to have syphilis in a presumably infectious state, and who are not permitted to marry, will not necessarily discontinue having sexual intercourse. . . .
>
> The only way to prevent congenital syphilis is to *treat the syphilitic mother during pregnancy*. . . . Premarital blood tests do not contribute materially to the prevention of congenital syphilis.
>
> Premarital blood test legislation tends to give legal support to popular misunderstanding of the significance of blood tests, and to perpetuate the notion that the problem of syphilis control can be solved by making blood tests. . . . Premarital blood test laws apply one single and inconclusive test for one single disease condition to the whole question of fitness to marry. This is poor premarital public education. . . .

In a provocative article Leider[272] ponders certain theoretic considerations in the planning of venereal disease control. Pointing out

271. Nelson, N. A.: Why Is a Pre-Marital Blood Test Law Unsound Legislation? Baltimore Health News **24**:127 (May) 1947.

272. Leider, M.: Theoretical Considerations in Venereal Disease Control Planning, Am. J. Syph., Gonor. & Ven. Dis. **31**:325 (May) 1947.

that the spread of the genitoinfectious diseases implies sexual promiscuity, he suggests that disregard for the sexual and moral adjuncts has led to errors or deficiencies in the control of venereal disease, which should be approached more as control of behavior. In this writer's opinion, "the control of venereal diseases is a social problem primarily, with incidental medical and moral aspects." Continent or strictly monogamous sexual habits are not considered to be ends impossible of attainment. If such social behavior had been characteristic of the members of the armed forces during the last war, "a great deal of lubricious fun would have been missed to be sure, but so would several million new cases of venereal disease, unnumbered illegitimacies, much juvenile and adult delinquency and a heritage and tradition of martial grossness."

SYPHILIS AND OTHER DISEASES

Yaws.—It is generally believed that in yaws late manifestations of the disease are comparatively rare. Osseous lesions, such as gangosa (rhinopharyngitis mutilans) and goundou (exostoses of the nasal and frontal bones), are now considered to be tertiary manifestations of yaws, but involvement of the cardiovascular and central nervous systems is almost unknown.

Smith,[273] while stationed in the Marshall Islands during World War II, was impressed by the ataxia of many of the native stevedores who had had long-standing infection with yaws. He could demonstrate none of the neurologic abnormalities of tabes dorsalis other than ataxia, but in 1 case there were changes in the joints in one knee and one ankle that were compatible with the Charcot type of arthropathy.

Padilha Goncalves[274] reports that it is occasionally possible to produce the lesions of pinta in patients with acute or latent yaws by experimental inoculation with T. carateum. Among 9 patients with yaws there were 2 in whom lesions of pinta developed. The fact that inoculations were unsuccessful in 7 is adduced as evidence of a partial immunity conferred by yaws against pinta.

Cancer.—Laitinen,[275] after analyzing 2,073 cases of cancer at the University Hospital in Helsinki, concludes that "syphilis has comparatively frequently an influence in the origin of cancer, but it is by no means one of the principal causes of it. Syphilis gives origin to cancer by means of prolonged irritation caused by local changes." In his

273. Smith, F. H.: Charcot-Like Joints in Yaws, U. S Nav. M. Bull. **46**: 1832 (Dec.) 1946.

274. Padilla Goncalves, A.: Sobre la transmision de pinta experimental a frambesicos, Bol. Soc. cubana de dermat. y sif. **3**:169 (Dec.) 1946.

275. Laitinen, H.: Ueber die Korrelation zwischen Syphilis und Krebs, Duodecim **34**:111, 1945.

material the incidence of syphilis in patients "at cancer age" in Finland was 1 to 2 per cent. Among the 2,073 patients with cancer the incidence of syphilis was 6.6 per cent. Concomitant syphilitic infection was most frequently present in patients with cancer of the female genital organs, lungs, anus and rectum, mouth and tongue. A higher incidence of syphilis was not apparent among patients with squamous cell carcinoma of the skin, cancer of the central portion of the digestive tract or cancer of the upper respiratory tract. Cancerous lesions developing in patients with syphilis progressed in a manner similar to those developing in nonsyphilitic persons, and there was no demonstrable difference between the two groups in their response to radiation therapy.

Genital Tuberculosis.—On rare occasions a primary tuberculous complex may occur on the skin or mucous membranes. There may then be a tuberculous ulcer, with involvement of the regional lymphatic channels and nodes. As Bjørnstad's [276] 2 cases illustrate, such tuberculous lesions may occur on the genitalia as a result of infection in venery. The diagnosis is established by histopathologic and bacteriologic examination of tissue after syphilis, lymphogranuloma venereum and chancroidal infection have been excluded. When, as in the 2 cases here reported, the sexual partner is known to have urogenital tuberculosis, the diagnosis is more readily apparent. Patients with tuberculosis of the genitourinary tract should be informed of the danger of contagion, particularly for sexual partners with negative reactions to the tuberculin test.

Sonck [277] describes a case in which a middle-aged man who had had tuberculous pleurisy, cervical lymphadenopathy and apparently benign pulmonary involvement (but no signs of involvement of the urinary tract) had, over a period of ten years, recurrent papulonecrotic tuberculids of the penis. The genital lesions were accompanied with recurrent keratoconjunctivitis, often appearing simultaneously with recurrences of the penile lesions.

The subject of tuberculosis of the penis has recently been reviewed by Lewis,[278] who records that the lesion may be either primary or secondary to pulmonary or genitourinary foci. Of 110 cases previously reported, in 72 the condition was the result of ritual circumcision. The lesion most frequently starts as a papule, which usually ulcerates. Because of its appearance, its clean base and the presence of induration,

276. Bjørnstad, R.: Tuberculous Primary Infection of Genitalia: Two Cases of Venereal Genital Tuberculosis, Acta dermat.-venereol. **27**:106, 1946.

277. Sonck, C. D.: A Case of Papulo-Necrotic Tuberculides on the Penis, Acta dermat.-venereol. **27**:45 (June) 1946.

278. Lewis, E. L.: Tuberculosis of the Penis: A Report of Five New Cases, and a Complete Review of the Literature, J. Urol. **56**:737 (Dec.) 1946.

tuberculosis of the penis readily is confused with primary syphilis. Treatment usually is unsatisfactory, and the prognosis is unfavorable.

Behcet's Syndrome.—To be differentiated from syphilis and other genitoinfectious diseases is the triple symptom complex which has come to be known as "Behcet's syndrome." This condition, named for the Turkish dermatologist who in 1937 [279] first integrated its several manifestations, is characterized by aphthous-like ulcerations of the oral and genital mucous membranes and a variety of ocular disturbances, the most characteristic of which is uveitis with hypopyon. Apparently, it encompasses the conditions which have been known as "ulcus vulvae acutum" and "periadenitis mucosa necrotica recurrens" and is to be distinguished from aphthous stomatitis, pemphigus and erythema multiforme.

The reported cases have involved young adults of either sex, who appear otherwise to be in good health. The genital and oral lesions, which usually appear first, are recurrent and resistant to treatment. Ocular involvement, though protean in its manifestations, usually is first manifested as an iritis or uveitis, with subsequent hypopyon and blindness.

The cause of Behcet's syndrome is not known, although it is probably of virus origin. Bacillus crassus, which is considered by some to be identical with Döderlein's bacillus and which has been found only in the genital lesions, appears to be either a secondary invader or, more probably, a nonpathogenic saprophyte. There is as yet no consistently efficacious therapy.

Katzenellenbogen,[280] who reports 3 cases in which the three symptoms were present, notes that in his patients the lesions on the oral mucosa had a predilection for the lower lip, that lesions on the genitalia consisted of sharp-edged ulcers with preference for the scrotum and that although the mucosal ulcerations healed after local therapy the ocular manifestations were resistant to all forms of treatment and led to blindness. Other lesions noted were erythema-nodosum-like nodules on the extremities, acneform eruptions and recurrent epididymitis. All 3 patients had unusual dermal sensitivity. Pustules formed at the site of puncture of the skin, and injection of any of a number of different substances was followed by erythema. Cowpox vaccination is suggested as a therapeutic procedure, presumably on the basis of possible virus antagonism.

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279. Behcet, H.: Ueber rezidivierende, aphthöse, durch ein Virus verursachte Geschwülste im Mund, am Auge und an den Genitalien, Dermat. Wchnschr. **105:** 1152 (Sept. 4) 1937.

280. Katzenellenbogen, I.: Recurrent Aphthous Ulceration of Oral Mucous Membrane and Genitals Associated with Recurrent Hypopyon Iritis (Behcet's Syndrome): Report of Three Cases, Brit. J. Dermat. **58:**161 (July-Aug.) 1946.

Curth's review [281] of "recurrent genito-oral aphthosis and uveitis with hypopyon" is the first in the American literature and the most complete thus far available. This author reports 2 additional cases in which bacteriologic studies yielded no clue as to the cause and in which various therapeutic measures (vitamin therapy, removal of foci of infection, vaccination, oral administration of sulfonamide drugs and injection of penicillin) were ineffectual.

Prosser Thomas' case report [282] is unique in that there was an associated thrombophlebitis and in that pathologic study of an excised eye is reported. There was complete detachment of the retina, with gross intraocular hemorrhage, chiefly subretinal. Marked patchy thickenings of the ciliary body and the choroid were evident, but there was no evidence that vascular thrombosis was the initial factor. O'Donnell [283] reports the association of Behcet's syndrome with epididymitis, geographic tongue and gastric symptoms.

Condylomata Acuminata.—In 1942 Kaplan [284] introduced a simple and effective method of treatment for condylomata acuminata, consisting of topical application of a 25 per cent solution of podophyllin in mineral oil.

Anderson [285] testifies to the efficacy of this treatment. Finding it difficult to keep the podophyllin suspension confined to the lesions, this author modified the method by using a 10 per cent tincture of resin of podophyllin applied with a cotton swab. The surrounding normal skin may be protected by an ointment consisting of 5 per cent aluminum powder in zinc oxide paste.

Sullivan and King [286] have treated 50 patients by a slight modification of Kaplan's method and have achieved rapid and spectacular clinical cures in 48, or 96 per cent. Within a few hours after treatment, signs of involution are manifested by shrinking, pallor and loss of moisture. In twenty-four to forty-eight hours the verrucous masses decrease rapidly in size, and they disappear within three to six days, with little or no residual scarring. Irritation of the adjacent mucous membranes occurs

281. Curth, H. L.: Recurrent Genito-Oral Aphthosis and Uveitis with Hypopyon (Behcet's Syndrome): Report of Two Cases, Arch. Dermat. & Syph. **54:** 179 (Aug.) 1946.

282. Prosser Thomas, E. W.: So-Called Triple-Symptom Complex of Behcet, Brit. M. J. **1:**14 (Jan. 4) 1947.

283. O'Donnell, J. M.: Behcet's Triple Syndrome, M. J. Australia **1:**730 (June 14) 1947.

284. Kaplan, I. W.: Condylomata Acuminata, New Orleans M. & S. J. **94:** 388 (Feb.) 1942.

285. Anderson, C. R.: Treatment of Condyloma Acuminatum with Resin of Podophyllin, Arch. Dermat. & Syph. **54:**66 (July) 1946.

286. Sullivan, M., and King, L.: Treatment of Condylomata Acuminata with Podophyllin, Bull. U. S. Army M. Dept. **6:**200 (Aug.) 1946.

in most cases, but this subsides promptly. Patients should be cautioned lest the podophyllin suspension be transferred by the fingers to the eyes.

Studying the mode of action of podophyllin, King and Sullivan [287] found that its application to normal skin produces unusual changes in the epidermis. There are alterations in nuclear pattern, with break-up of chromatin masses and production of pyknotic fragments as well as cytoplasmic changes consisting of swelling, shrinkage from the cell membrane, hydrops, delicate fibrillation and alterations of staining reactions. Histologic examination of condylomas in the process of involution following applications of podophyllin showed numerous such "podophyllin cells."

Suspensions of colchicine in oil, applied in a similar manner, appeared superior to podophyllin in the treatment of condylomata acuminata. Neither was effective when applied to verrucae vulgares or other lesions with extensive keratinization, which suggests that the penetrating power of the drugs is slight. The mode of action of locally applied podophyllin and colchicine seems to be similar. There is a direct, immediate degenerative action, with resultant death of cells.

Finkle and Frishwasser [288] warn that severe balanitis may complicate the use of podophyllin for condylomata acuminata. They recommend that when 25 per cent podophyllin in mineral oil is used it should be removed from contact with the skin and mucous membranes within five hours.

Other Genital Lesions.—That ulcerative lesions of the genital mucous membranes may be caused by Micrococcus tetragenus has been shown by Pinck and Zhentlin.[289] Because of the low virulence of this organism, infection ordinarily occurs subsequent to a predisposing disease which reduces the resistance of the host.

Herpes progenitalis is seldom recognized in women, though actually it is not uncommon. Slavin and Gavett [290] report 3 cases of vulvovaginitis due to herpes virus in which the diagnosis was proved by isolation of the virus and demonstration of a rising titer of circulating antibodies. The clinical picture was distinctive. Superficial erosions involved considerable areas of the labia minora, adjacent labia majora and vaginal mucous membranes. The ulcers were tender and were usually covered

287. King, L. S., and Sullivan, M.: The Similarity of the Effect of Podophyllin and Colchicine and Their Use in the Treatment of Condylomata Acuminata, Science **104**:244 (Sept. 13) 1946.

288. Finkle, T. H., and Frishwasser, E. J.: Treatment of Penile Condylomata Acuminata with Podophyllin, J. Invest. Dermat. **8**:199 (April) 1947.

289. Pinck, B. D., and Zhentlin, B.: Penile Ulcer Caused by Micrococcus Tetragenous, Bull. Johns Hopkins Hosp. **80**:198 (April) 1947.

290. Slavin, H. B., and Gavett, E.: Primary Herpetic Vulvovaginitis, Proc. Soc. Exper. Biol. & Med. **63**:343 (Nov.) 1946.

by a grayish yellow membrane. Some of the lesions appeared to have been autoinoculated.

Circumcision and Venereal Diseases.—Wilson,[291] who has reviewed the records of 1,000 consecutive cases at a Canadian Army Venereal Disease Treatment Center, reports that the incidence of all venereal diseases was significantly higher among uncircumcised males than among those who had been circumcised. Ninety per cent of all his cases of primary syphilis and 73.5 per cent of his cases of gonorrhea involved uncircumcised persons. There were 22 cases of balanitis and 18 cases of venereal warts, all in the uncircumcised group.

291. Wilson, R. A.: Circumcision and Venereal Disease, Canad. M. A. J. **56**:54 (Jan.) 1947.

Correspondence

IMMERSION HYPOTHERMIA

To the Editor:—In the January 1947 number of the ARCHIVES is published an article by Major Edgar Wayburn, entitled "Immersion Hypothermia." In it a citation is made which I believe should not pass without comment. I refer to the discussion, on page 90, of the results claimed by Germans who experimented on their prisoners in concentration camps. It is now generally known that such experiments were done and that the most horrible crimes in this respect were committed. It has been a matter of discussion in some quarters whether the results obtained in such a way should be discarded or eventually made use of. My personal opinion is that nothing can be gained by suppressing really valuable scientific knowledge because it has been acquired in a criminal way. The suffering of the victims cannot be alleviated by our refusing to acknowledge the scientific data which their misery may have yielded. I am firmly convinced, however, that the data acquired by human experiments in German concentration camps are in general without any scientific value whatever. I cannot judge the results cited by Dr. Wayburn in his paper, for I was not a direct witness to these or other human experiments. On the other hand, a nearly two year stay as prisoner in the medical service of the concentration camp at Buchenwald has given me some knowledge of the value of scientific data gained in these circumstances. Often experiments were supervised by nonmedical, unsufficiently trained personnel. But, what is more important, the men who had to compile the data were, and could not be, primarily concerned with their exactness. Their first interest was to give their SS guards the results they were looking for. It may be difficult for those who have never known life as a prisoner in a German concentration camp, or even in German-occupied territory, to understand to how few primitive principles life may be reduced. But, certainly, objective, unbiased scientific experimentation and gathering of data for the SS were not among them.

The scientific value of the "extraordinary series of experiments" cited by Dr. Wayburn therefore seems doubtful. Besides, I do not think that experiments such as these should be cited without once more drawing attention to their unpardonable nature. Furthermore, the perpetrators of these crimes should not be mentioned among decent scientists in a list of authors, as has been done here. Neither should they be alluded to as German investigators. Let us not forget that men the like of these are now being tried for crimes against humanity.

Human life and health are, or at least should be, still too valuable to experiment on. This will be accorded by every one in the face of

the aforementioned experiments. I believe it should also be seriously considered by those who, as seems to be a growing custom, experiment with human volunteers.

R. J. HAMBURGER, M.D., Netherlands.

Alkmaar Holland, Wilhelminalaan 8.

To the Editor:—My sympathy goes out to Dr. R. J. Hamburger and any other human being unfortunate enough to be confined in a German concentration camp. I have no objection to the publication of his letter about the article "Immersion Hypothermia," published in the January 1947 issue of the ARCHIVES.

As he says, "Nothing can be gained by suppressing . . . scientific knowledge because it has been acquired in a criminal way." I did not comment on the reliability of the data obtained by the German investigators (investigators they were for good or evil) except to remark that certain data agreed with my own findings. I see no further need to comment now.

490 Post Street.

EDGAR WAYBURN, M.D., San Francisco.

News and Comment

GENERAL NEWS

Third Interamerican Cardiological Congress.—The Interamerican Society of Cardiology has authorized the meeting of the Third Interamerican Cardiological Congress to be held in Chicago, at the Michael Reese Hospital, from June 13 to June 17, 1948. This meeting will take place immediately before the annual meeting of the American Heart Association, June 18 and 19, and the Annual Session of the American Medical Association, the week of June 20. Inquiries regarding the congress may be addressed to the offices of the Third Interamerican Cardiological Congress, Michael Reese Hospital, Chicago.

SOCIETY NEWS

Brazilian Society of Cardiology.—The fourth annual meeting of the Brazilian Society of Cardiology was held in São Salvador da Bahia the week of July 1 to 7, 1947. The main subject of the meeting was hypertensive heart disease and rheumatic heart disease.

The 1948 meeting of the society will be held in Porto Alegre. The subjects to be discussed are rheumatic heart disease and social assistance of the patient with cardiac disease.

The following officers have been elected for the current year: Prof. Otavio Magalhães, president; Dr. Aldo Chaves, vice president; Prof. Roberto Menezes de Oliveira, general secretary; Prof. Horacio Kneese de Mello, second secretary; Dr. Emiliano Lourenço Gomes, treasurer, and Prof. Jairo Ramos, director of the *Arquives.*

CORRECTION

In the article by Dr. Clifford H. Peters and his associates entitled "Neurologic Manifestations of Infectious Mononucleosis, with Special Reference to the Guillain-Barré Syndrome" in the September issue (ARCH. INT. MED. **80**:366, 1947) the number "9,700" in the fifth line of the fifth paragraph of the "Report of Cases" on page 367 should read "97," and the number "36,000" in the seventh line of the second new paragraph on page 368 beginning "On September 24," should read "36."

Book Reviews

Quantitative Clinical Chemistry: Interpretations. By John P. Peters, M.D., and Donald D. Van Slyke, PH.D., Sc.D. Second edition. Volume 1. Price, $7. Pp. 1,050, with 62 illustrations. Baltimore: Williams & Wilkins Company, 1946.

The first volume, "Interpretations," of the new edition of Peters and Van Slyke's book deals with four topics. Part I covers the subject of energy metabolism. Slightly more space is devoted to this subject in the new edition than in the previous one. Many of the tables contained in the first edition have been omitted. Articles written as recently as 1945 are mentioned, and the presentation of most topics in this section has been revised. A few minor subjects are presented, as in the first edition. Some new topics have been added; these include a discussion of the estimation of metabolism from perspiration.

Part II is concerned with carbohydrate metabolism. This section is much larger than that in the previous edition and has been subdivided into chapters dealing with chemistry and physiology and with clinical application of existing knowledge concerning carbohydrate metabolism. This section represents a comprehensive treatment of the subject, including recent advances in knowledge concerning the mechanism of carbohydrate degradation in the body.

The section on lipids represents a vast improvement over that in the preceding edition. The literature has been covered thoroughly, and most experimental observations on the subject are recorded. Included under the topic of lipids are chapters on steroid hormones and fat-soluble vitamins. One might question the wisdom of publishing as an accepted fact the structural formula of a steroid nucleus attached to vitamin C when the only supporting reference given is to the unpublished work of one author.

The fourth part of the book deals with the various aspects of protein metabolism. Some of the experiments with isotopes which give an insight into the dynamics of protein metabolism are included in this section.

In general the style of presentation of the subject matter is much the same in this as in the previous edition. Medical students who have complained bitterly in the past when referred to this book will find no less cause for lamentation in the future. However, those who seek access to an exhaustive résumé of studies made in a given field will be saved much time and effort by consulting this work before looking elsewhere. It is a great satisfaction to the investigator to know that there is available in the English language such a reliable and comprehensive treatment of these subjects. It is hoped that the new edition will prove to be more substantially bound than its predecessor.

The Nature of Disease up to Date: An Outline of a Unitary Theory. By J. E. R. McDonagh, F. R. C. S. Price, 15s. net. Pp. 168. London: William Heinemann, Ltd.; New York: Grune & Stratton, Inc., 1946.

According to "Who's Who," 1946, the author of this monograph is a British medical consultant who, at the same time, is engaged in medical research. The statement appears in this usually reliable source of information that his investigations have resulted in the discovery of the cause of syphilis and of the common cold

and influenza and in the introduction of several preventive and combative remedies for use in the various manifestations of disease. He has literary attainments as well, having published several books, and, above all, an ambition to correlate all diseases, whatever their nature, in relation to his interpretation of their physico-chemical process.

The present volume is a continuation of three others which also deal with the nature of disease. The same two criticisms are pertinent of the third member of the series as the *Lancet* (1021 [Nov. 15] 1924) noted of the first: It is remarkably tedious to read, and in parts it is impossible to understand. Nor can American readers be encouraged to embark on it without being reminded of an earlier comment, still valid, which the *Lancet* expressed to prospective readers when the first volume was reviewed, namely, that the author uses his imagination too frequently and too freely.

Eye Manifestations of Internal Diseases. By I. S. Tassman, M.D. Second edition. Price, $10. Pp. 614, with 243 illustrations, 24 in color. St. Louis: C. V. Mosby Company, 1946.

The appearance of a second edition of this book in a relatively short time after the first edition was published indicates that the book has been exceptionally well received. The favorable reception is well merited. .

The second edition has been enlarged by the addition of a description of a number of new diseases and an enlargement on the treatment of various conditions. Just how valuable the latter addition will be is questionable. After all, the book is primarily a publication on the ocular expressions of internal disease, and the treatment of internal diseases should be left to the internist in the great majority of cases.

The reviewer would much prefer to see the space allotted to many unusual and rare diseases and their treatment, also more reproductions of eyegrounds. The internist is primarily interested in the eyegrounds, which are probably the most frequently examined by him in conjunction with a study of the eye. He is rarely interested in local disorders of the eye, which have a distant or questionable relation to internal medicine.

Narco-Analysis: A New Technique in Short-Cut Psychotherapy, A Comparison with Other Methods and Notes on the Barbiturates. By J. Stephen Horsley. Price, $2.50, 8s. 6d. Pp. 134. London: Oxford University Press, 1943; New York: Oxford University Press, 1944.

This brief monograph is a succinct outline of "a new technique in short-cut psychotherapy." The method, which the author began to use in 1931 and perfected in the urgency of modern war, consists in the induction of hypnosis in a patient already narcotized with barbiturates, so that he reveals hitherto repressed, emotionally traumatic experiences and becomes accessible to the physician's therapeutic suggestions. A further, deep narcosis may be added by the injection of additional barbiturates to secure a restful sleep of twelve or more hours.

The author is a pioneer in the field, and his method, variously modified by many others, has proved to be one of the popular, if not unfailingly successful, psychiatric procedures evolved during the war. His exposition in this little volume is lucid and instructive. He nevertheless makes it clear that the personal influence of the physician on the patient is of greater importance than any mere technic. The book can be recommended as an excellent introduction and the appended bibliography as a guide to the physician in his wider pursuit of the subject.

Lehrbuch der Urologie. By J. Minder, M.D. Price, 37.50 Swiss fr. Pp. 348. Bern, Switzerland: Buchhandlung und Verlag Hans Huber, 1946. Distributor in United States, Grune & Stratton, Inc., New York.

This is a concise and complete textbook on urology. The reviewer was especially impressed with the marginal paragraph headings which make it simple to find a particular paragraph or subhead when using the book as a reference. The illustrations are not as numerous or in many instances as good as in most American textbooks, although the diagrams are clear and easily understandable. The book follows a logical sequence and is an excellent textbook for any medical student who can read German fluently.

The reviewer was also particularly impressed with the small amount of importance and stress which is laid on the subject of transurethral resection and also with the relative unimportance with which hormonal therapy and castration in the treatment of carcinoma of the prostate is handled. Apparently in the eyes of Professor Minder these two subjects have not reached the same degree of popularity or importance as they have in this country.

This is a good reference text for both the urologist and the general practitioner.

Textbook of Medical Treatment. Edited by D. M. Dunlop, L. S. P. Davidson, and J. W. McNee. Fourth edition. Price, $8. Pp. 944, with 38 illustrations. Baltimore: Williams & Wilkins Company, 1946.

This is a notably popular book, requiring new editions almost every other year. It made its appearance in 1939. The *New England Journal of Medicine* (**223**:43 [July] 1940) was among the first to recognize it as an outstanding text. Reviews of earlier editions in *The Journal of the American Medical Association* and in the ARCHIVES OF INTERNAL MEDICINE were also complimentary.

The second edition appeared in 1942 and the third in 1944, and now the fourth is at hand. This is much like its predecessors but is brought up to date by careful editing and occasional new chapters.

As the ARCHIVES (**75**:144 [Feb.] 1945) has stated, the volume presents an excellent and conservative statement of modern treatment in internal medicine. It is especially interesting as showing the almost complete harmony now evident in British and American therapeutic practice.

The latest edition promises to maintain for the book the prominent position which it has attained in former printings. One can safely prophesy its continued success.

Office Endocrinology. By Robert B. Greenblatt, M.D. Third edition. Price, $4.75. Pp. 320, with 71 illustrations. Springfield, Ill.: Charles C Thomas, 1947.

This book contains a great deal of useful information. It is in no sense a systematic or comprehensive textbook of endocrinology. The major portion consists of brief chapters dealing with certain problems which confront the physician, especially in female endocrinology, for example the chapters with the following headings: "The Mechanism of Uterine Bleeding," "Dysmenorrhoea," "Hormonal Therapy of Fibromyomas of the Uterus," "Acne in Adolescence," and "Endocrine Headaches." There are chapters on "Hormonology," in which the availability and use of specific preparations are dealt with. There are numerous excellent illustrations. The book should be useful to the general practitioner, although in a subject of this sort not all will agree entirely on the best method of procedure.